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THE DIAGNOSIS AND TREATMENT OF TRACHEAL AND ESOPHAGEAL OBSTRUCTION DUE TO CONGENITAL VASCULAR RING

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PRIOR to 1925, the congenital anomaly characterized by a double aortic arch was reported as a pathologic curiosity. In that year Arkin[1] wrote the first roentgenologic account of this condition. The patient was a 50-year-old man. The accuracy of this observation was verified at post-mortem examination.

Medical treatment of this condition has not been satisfactory. The symptoms are frequently distressing and progressive. Those patients fortunate enough to survive may be forced to subsist on soft solid and liquid diets. Others die of suffocation or repeated pulmonary infections. Some succumb as a result of a tracheotomy, which obviously cannot be expected to provide relief.

In 1933, Sprague and associates[15] stated their belief that surgical intervention "presents intriguing theoretical possibilities" and was justified in patients with this anomaly if dyspnea or dysphagia were predominant symptoms. The following quotation is from their paper:

> So far as we know there has never been any surgical approach to the relief of pressure symptoms, but it presents intriguing theoretical possibilities. . . . Specifically, the hope in such cases would be to find an obliterated ductus arteriosus or remnant of the left fourth arch which could be divided or removed to allow more anterior and lateral mobility of the esophagus and trachea, even though the aortic arch continued to exert pressure from behind.

The following case reports represent two examples of surgical intervention for this condition.

CASE HISTORIES

CASE 1.—L. B., a 3½-month-old male, entered the Massachusetts General Hospital on May 17, 1945, because of paroxysmal cough and wheezy breathing first noticed ten days after birth.

From the Children's Medical and the Surgical Services of the Massachusetts General Hospital, Boston.

Past History.—The patient was born at term. Delivery was normal. The birth weight was 8 pounds, 7 ounces. The mother was not aware that the child had any unusual signs or symptoms while in the hospital, nor were any listed in the hospital record. The infant's diet was adequate, except that no vitamin D was given.

On the tenth day of the child's life he experienced a severe paroxysm of coughing, during which he became cyanotic. From that time on he had recurring attacks, sometimes four or five each day. They usually lasted only a few minutes and tended to subside abruptly. Those that occurred with feeding were accompanied occasionally with vomiting. The respirations were of a "wheezy" character, but they became normal while he was asleep. When the child was 1½ months old the family physician made a diagnosis of "croupy bronchitis."

By the time the baby was 2½ months old, the paroxysms of coughing and almost continuous wheezing had become more severe and he was admitted to a hospital. On admission, the temperature was found to be 101° F. rectally. A roentgenogram of the chest showed marked increased density of both hilar regions. A diagnosis of virus pneumonia was made. The child continued to have a low level of fever for the next twelve days. He breathed quietly while asleep but wheezed while he was awake, especially during feedings. Sulfadiazine was administered for seven days without benefit. In spite of his difficulties, however, he continued to gain weight.

On the twenty-ninth hospital day the baby became cyanotic while being fed and was transferred to the Massachusetts General Hospital.

Physical Examination.—On admission to this hospital the child was in no acute distress. He was a well-developed, well-nourished, 3½-month-old infant. The anterior fontanel was open. His respirations were noisy, and if he became excited he developed inspiratory stridor. There were no signs of acute upper respiratory infection. The trachea was in the midline.

The chest was symmetrical and both sides expanded equally. There was no Harrison's groove. The chest circumference was 16 inches. There was slight inspiratory supraclavicular, sternal, and intercostal retraction. Percussion over the lung fields revealed no abnormality. The breath sounds were obscured by loud inspiratory and expiratory noises transmitted from the trachea. A direct laryngoscopy was performed by Dr. John Richardson and the larynx was found to be entirely normal.

His weight was 14 pounds 5 ounces, length, 26 inches. His temperature was 99.8° F., and his blood pressure was 100/50.

Laboratory Data.—The urine was negative. The red blood cell count was 3.56 million; hemoglobin, 9.75 Gm. per cent; white blood cell count, 12,750, with normal differential. Tuberculin test 1:1,000 was negative and the Hinton test was negative. The serum calcium was 11 mg. per cent; inorganic phosphorus, 6.5 mg. per cent; alkaline phosphatase, 11 Bodansky units; nonprotein nitrogen, 32 mg. per cent; and serum protein, 5.5 Gm. per cent.

Roentgenologic examinations of the esophagus with the aid of barium showed an indentation posteriorly at the level of the aortic arch (Fig. 1). Slightly caudal to this there was an indentation of the right lateral margin of the esophagus (Fig. 2). Taking the child's symptoms into consideration, these findings suggested a right-sided aortic arch with a vascular ring about the esophagus and trachea. Nothing pathognomonic was noted in the neck, upper mediastinal shadow, or chest by plain chest films. Roentgenograms of the wrist showed no evidence of rickets.

Course.—The child's temperature remained normal. He wheezed continuously and had frequent episodes of coughing. He took most of his feedings well, but at one feeding he had considerable difficulty in swallowing, and became limp and cyanotic. However, he recovered in a few minutes.

Diagnosis.—Several causes of stridor in infants were considered at first. The observed concentrations of serum calcium, inorganic phosphorus, and phosphatase excluded a diagnosis of neonatal, rachitic, or hypoparathyroid tetany. Rickets was further excluded by the negative roentgenographic examination of the wrists.

The laryngoscopic examination readily excluded any abnormality of the larynx, and roentgenograms of the chest proved that the difficulty was not caused by absence of tracheal rings.

The diagnosis of right-sided aorta and congenital vascular ring constricting the esophagus was therefore established on the basis of roentgenologic examination of the esophagus with the aid of barium.

Dr. Paul D. White concurred in the opinion that an anomalous vascular ring was the probable cause of the respiratory and esophageal difficulties, and agreed that operative intervention was justified.

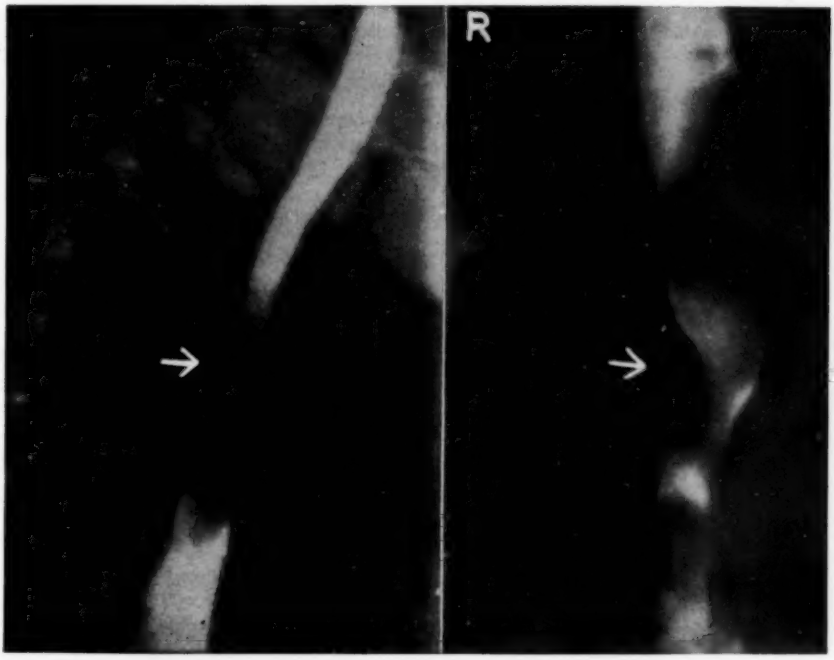


Fig. 1. Fig. 2.

Fig. 1.—Case 1. Lateral view of esophagus following ingestion of barium. Arrow points to posterior indentation.

Fig. 2.—Case 1. Postero-anterior view of barium-filled esophagus. Arrow indicates the lateral impression caused by right aortic arch.

Operative Findings and Procedure.—On July 12, 1945, under ether-oxygen intratracheal anesthesia, an operation was performed. The incision was made through the fifth intercostal space on the left side. When the pleura and pericardium overlying the great vessels had been retracted, an unusual vascular arrangement was encountered (Fig. 3). There was a right or dorsal aortic arch which arose from the usual location at the base of the heart. This ascended and curved over the right main bronchus. It proceeded posteriorly and behind the esophagus, emerging from the left posterolateral aspect of that structure. Here it was joined by another, much smaller vessel, which arose from the first described vessel about one centimeter above its cardiac origin and passed in front of the trachea and esophagus. From this junction the artery descending in the normal course of the descending aorta along the left side of the vertebral column.

It was evident that these two vessels represented a doubled aortic arch of which the dorsal component carried the major blood load. The anatomy to the right of the trachea and esophagus could not be clearly visualized, but it appeared that the right common carotid and subclavian arteries arose separately from the larger vascular trunk on that side. The anterior vessel, or left aortic arch, sloped slightly to the left and posteriorly. At approximately its midportion there arose a long slender artery which extended through the superior mediastinum to the dome of the left chest where it branched into the common carotid, subclavian, and internal mammary arteries. This vessel was actually a left innominate artery. A patent ductus arteriosus connected the undersurface of the left arch with the pulmonary artery on that side at a point approximately one centimeter distal to the origin of the left innominate artery. The left recurrent laryngeal nerve passed beneath the anterior arch just lateral and posterior to the ductus. It then proceeded superiorly along its usual pathway.

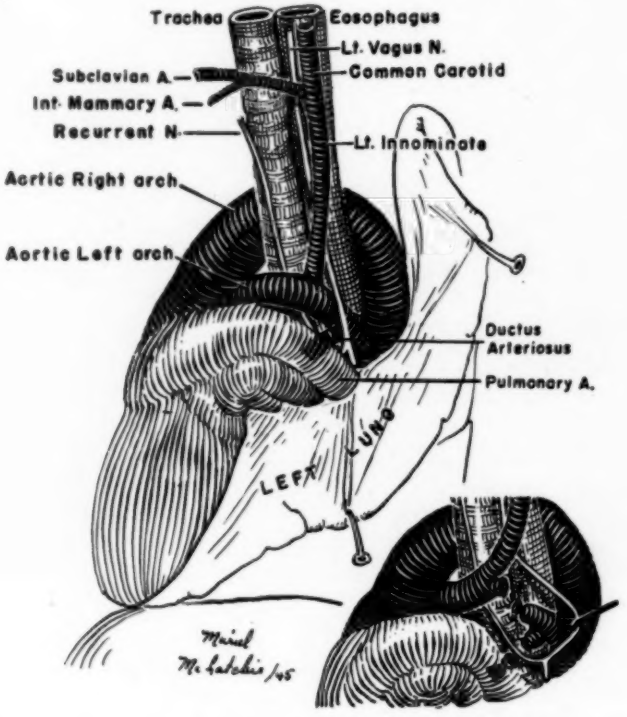


Fig. 3.—Case 1. Diagram illustrating left anterolateral view of the great vessels and their relations. Inset to demonstrate interruption of the vascular ring following ligation and division of the left arch and the patent ductus arteriosus.

After this anatomy was surveyed, the ductus arteriosus was occluded by external pressure, and no untoward effect was noted. It was then divided between two ligatures of braided silk. The ventral component of the double aortic arch was similarly compressed at a point between the innominate artery and the stump of the ductus. No appreciable change of vital signs was observed. The color of the upper extremities remained normal and the radial pulses did not change. Division of this vessel between ligatures was therefore performed at the site of compression. A sudden shift in the great vessels occurred immedi-

ately (Fig. 3 inset). The left innominate artery retracted superiorly and anteriorly. The exposed portion of the dorsal aortic arch receded slightly posteriorly and to the right. The trachea and esophagus appeared to bulge forward and to the left. They were now completely free from constriction. The operation was terminated in the usual manner. The patient withstood the procedure well and was returned to his crib in good condition. No change in the color or temperature of the extremities was ever noted.

Postoperative Course.—Postoperatively, the patient made an uneventful recovery. He received oxygen on his first postoperative day. After he had been on the ward for a few hours, he tolerated a 2 per cent whole milk and Karo formula. His airway was kept clear by frequent aspirations of mucus from his nasopharynx. The temperature rose to 101° F. on the first postoperative day, and returned to normal two days thereafter. It remained normal during the remainder of the child's stay in the hospital. The respiratory rate was 50 on the first postoperative day, but soon dropped to 30, and this rate was maintained until discharge. The character of his respirations was noticeably improved, except during excitement when there was a tendency to wheezing. While crying, he became slightly cyanotic, but he suffered no dysphagia and took his feedings without any of the alarming symptoms observed preoperatively. The respirations appeared to be entirely normal while he was sleeping and when he was undisturbed.

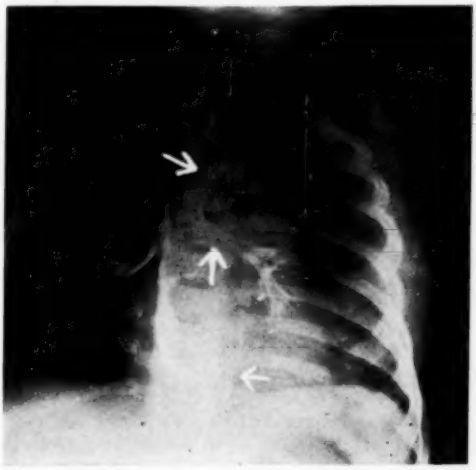


Fig. 4.—Case 1. Postoperative lipiodol bronchogram with coincidental filling of the esophagus. Arrows indicate right lateral impression of the esophagus and narrowed left main bronchus (see text). An arrow also points to the descending aorta on the left.

Postoperative roentgenograms of the chest showed both lung fields clear; the upper mediastinal shadow was not abnormal. A bronchogram was performed on July 23, 1945, under ether anesthesia (Fig. 4). The right, lateral margin of the trachea was slightly indented by the aortic arch on that side. Just distal to this impression the trachea deviated sharply to the right. The left main bronchus branched from the trachea at a more acute angle than normally. Narrowing of the midportion of this bronchus was noted. The main bronchus on the right was normal, as were all secondary bronchi. Some lipiodol spilled over into the esophagus and the indentation of its right lateral aspect, noted before operation, was still present. On physical examination, rhonchi could still be heard, apparently transmitted from the laryngeal region, but otherwise nothing unusual was found. He was discharged July 28, 1945, to be followed in the Outpatient Department.

The baby did well at home and gained weight steadily. He experienced no dysphagia. The cry, which had been somewhat weak, became stronger. The wheezing tendency diminished until he developed an upper respiratory infection, when the wheeze became more noticeable. In spite of this infection he continued to eat well and gained weight. Roentgenograms of the chest revealed normal heart and lungs.

Embryologic Considerations.—The anomaly found in our first patient is quite unique when compared with anatomic descriptions of double aortae in the literature. Whereas the majority of reports state that the left subclavian and common carotid arteries arise separately from the ventral or left arch,[16] (Fig. 5, *B*) these vessels in this instance branch from an innominate artery which in turn originates from the left arch. To explain the development of such an arrangement, it is necessary to present a different concept of embryologic development from that which has usually been proposed.

Congdon[5] has described fully the evolution of the aortic arch system in the human embryo. Only the essentials of this subject will be presented here.

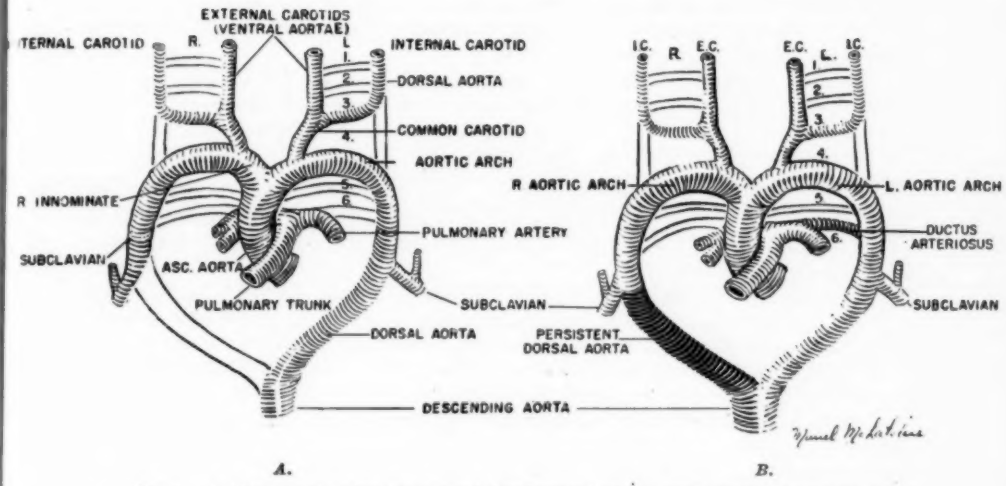
In the second week of embryonic life, there exists a single chambered heart. On each side of this there is an ascending or ventral aorta, an aortic arch, and a dorsal aorta. Toward the end of the fourth week (5 mm. embryo) the ascending segments unite to form the truncus arteriosus and the dorsal aortae combine to form a common descending aorta at a lower somatic level. Six aortic arches soon develop on each side. These connect the anterior and posterior trunks (Fig. 5, *A*). They do not appear at the same time, and some of them regress completely. While they are present, the anlagen of the trachea and esophagus are encircled. Normally, the external carotid arteries represent the surviving elements of the ventral paired aortae. The internal carotid arteries are derived from the third arches and the persisting cephalic portions of the original dorsal paired aortae. The sections of the dorsal aortae which lie between the third and fourth arches disappear. The proximal portion of the right ventral aorta becomes the right innominate artery. The subclavian artery on that side is derived from the fourth right arch, a persisting segment of the right dorsal aorta, and usually the sixth intersegmental artery. On the left, the fourth arch becomes the definitive aortic arch which continues as the descending aorta. The pulmonary arteries are derived from the proximal portions of the sixth arches and their branches. Only on the left does the distal half of the sixth arch persist. This becomes the ductus arteriosus. When the truncus arteriosus divides sagittally, the pulmonary and aortic systems become separated. All arches not mentioned disappear completely.

Before the primitive dorsal aortae fuse, each gives off about thirty dorsal branches. With the union of these aortae the development of posterior paired vessels can be appreciated. These are arranged between the somatic segments and are designated as intersegmental arteries. Some of them later disappear while the remainder form the main stems of the lumbar, intercostal, and subclavian arteries. It should be noted that the sixth intersegmental arteries are usually incorporated in the subclavian arteries on both sides.

With the above information as a background, the embryology of our case can be explained briefly (Fig. 6). The right fourth aortic arch persisted in entirety and became the main blood conveyor to the descending aorta. The left fourth arch also remained and thus a permanent vascular ring about the esophagus and trachea was formed. The extremely unusual feature in this anomaly was the survival of the primitive left dorsal aorta between the third and fourth arches. From this arose the first intersegmental artery which ultimately became the first portion of the left subclavian system (Fig. 7). Due to another rare coincidence, this persistent dorsal aortic segment also became the sole supplier of blood to the left side of the head. This resulted from an atresia of the left ventral aorta between the third and fourth arches. The development of a left innominate artery is therefore explained.

CASE 2.—A. F., a 9-month-old male, came to the hospital for the first time in October, 1942, because of cough first noticed at the age of two weeks.

Past History.—The child was born at term by cesarean section. His birth weight was 7½ pounds. There was no neonatal distress, jaundice, or cyanosis. He was formula-fed from the start, received adequate vitamins, and gained well.



A. *B.*

Fig. 5.—*A*, diagram showing the normal development of the great vessels about the heart (see text). *B*, arrangement of the embryonic vessels in the most common type of double aorta. A patent ductus arteriosus is often found with this type of anomaly.

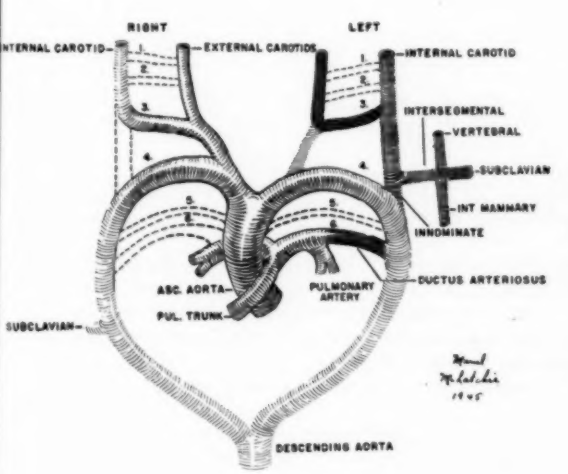


Fig. 6.

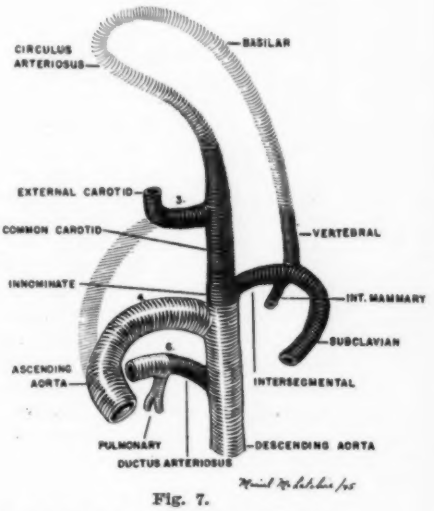


Fig. 7.

Fig. 6.—Diagrammatic ventral view of aortic system in Case 1 to show the embryonic development of the great vessels (see text).

Fig. 7.—Lateral view of the left aortic arch system to show the development of the left innominate artery in Case 1 (see text).

At the time the child was discharged from the maternity hospital, his mother noticed that he had a persistent loose cough which was most noticeable at night and in the morning. Two weeks before he was brought to the hospital the baby's cough became worse. He started to vomit part of his formula after each feeding.

Physical Examination.—The child was well developed and somewhat obese. He breathed noisily and had a continuous loose cough. The throat was diffusely injected and there was a moderate amount of mucus in the pharynx. The chest expanded equally. There was a mild degree of funnel chest. The percussion note was not impaired. On auscultation, musical and coarse râles were heard over both lung fields.

He weighed 19 pounds. His temperature was 99.8° F., respirations 36, pulse 100. The blood pressure was 85/50. The remainder of the physical examination was not remarkable.

Bronchoscopic examination revealed a normal appearing larynx, trachea, and bronchi. No foreign body was seen.

Laboratory Data.—The Hinton test was negative, the tuberculin test 1:1,000 was negative, and the urine was negative. The white blood cell count was 13,000, with normal differential; the red blood cell count was 4.3 million, and hemoglobin was 13.5 Gm. per 100 c.c.

Roentgenogram of the chest revealed a prominence of the upper mediastinal shadow on the right.

Course.—The infant was quite uncomfortable during his hospital stay. He coughed frequently, especially during and after feedings. Following the bronchoscopy, his temperature rose to 104° F. and he developed a purulent left otitis media. This infection responded well to sulfadiazine, and his temperature returned to normal within three days. The child was discharged to be followed in the Outpatient Department.

Second Admission.—The patient returned to the hospital two weeks later with a chief complaint of fever and cough. His mother stated that the child was vomiting most of his feedings. He was found to have a pneumonia of the left lower lobe which responded to sulfadiazine.

Course.—During the next fourteen months the patient returned frequently to the Outpatient Department. He developed another attack of purulent otitis media of the left ear, but otherwise did well. However, his cough persisted off and on, and it was noted that he had a slight wheeze when he became excited. The depression of the sternum progressed somewhat. X-rays of the chest showed no appreciable changes.

Third Admission.—On Feb. 18, 1944, at the age of 2 years, the child was brought to the hospital again with a chief complaint of more pronounced cough and fever of approximately three weeks' duration. He had vomited after most of the coughing paroxysms and had lost approximately three pounds.

The child was fairly well developed but looked pale. He weighed 24½ pounds. His temperature was 99.6° F., pulse 132, and blood pressure 88/60. He had a peculiar gagging cough which appeared to be productive. The throat was diffusely injected. The trachea was shifted to the right. The chest was hyperresonant to percussion. There were numerous squeaks, groans, and râles, particularly over the right lower lobe posteriorly. The funnel chest was present as before. No heart murmurs were noted. The remainder of the physical examination was essentially negative.

The white blood cell count was 33,000 with 75 per cent polymorphonuclear cells, red blood cell count was 4.8 million, hemoglobin, 15 Gm. per 100 c.c. Tuberculin test 1:100 was negative.

Roentgenogram of the chest showed no change from the previous examinations. The question of a right-sided aorta was considered. Consequently, a barium swallow was done which confirmed the previous findings of displacement of the superior mediastinum to the right. But it also showed narrowing of the trachea at the level of the aortic arch posteriorly and on the right, probably due to pressure. The arch of the aorta appeared to be in normal position. A right-sided arch could not be definitely excluded, but in such an event it would have to be a double aorta encircling the esophagus and trachea. The lung fields had not changed in appearance since the last observation nor had the funnel-chest deformity.

Course.—The child's upper respiratory infection subsided after treatment with sulfadiazine. Bronchoscopy was performed, but so much secretion was encountered that it was difficult to see the bronchi. Lipiodol was injected, but the amount was insufficient to give good pictures.

Twenty-four hours following the bronchoscopy, the child developed marked respiratory distress. Only temporary relief was afforded by bronchoscopic aspiration of the excessive mucous; therefore, a tracheotomy was done.

The child continued to have respiratory distress and ran a temperature up to 103° F. On the twelfth day after the operation, an esophagotracheal fistula developed. Administration of fluids by mouth was stopped and a gastrostomy was performed. Administration of sulfadiazine was continued. An adequate caloric intake was maintained through the gastrostomy.

At the end of four months the esophagotracheal fistula had healed, the tracheotomy tube was out, the gastrostomy wound had healed, and the child was discharged to a convalescent home.

He was seen on several occasions in the Outpatient Clinic and the parents insisted that he was quite well, though he continued to cough intermittently and to have some recurring upper respiratory infection. No mention was made of distress on feeding.

A roentgenogram in June, 1945, revealed very little change in the appearance of the chest.

Fourth Admission.—The child was readmitted to the hospital in January, 1946. He was then 4 years old. He was able to eat only liquids or strained foods and even with these he vomited two or three times at mealtime. His mother had not noticed any cyanosis. She admitted that he wheezed audibly when excited. He had had frequent upper respiratory infections from which recovery was slow.

The child was 39 inches in height and weighed 37 pounds. His blood pressure was 110/50. He had a marked funnel-chest deformity. The teeth were badly decayed. There were well-healed gastrostomy and tracheotomy wounds. There was inspiratory retraction of the sternum when he was excited. A systolic murmur was heard one inch to the left of the sternum. This was transmitted to the left axilla and was best heard to the left of the sternum between the second and third interspace. Femoral pulses were present. Examination of the lungs was not remarkable.

Roentgen examination and x-ray films confirmed the previous impression of a vascular ring encircling the trachea and esophagus. A barium swallow showed a characteristic picture of a double arch of the aorta. The esophagus at this level was seen to be deformed both posteriorly and anteriorly due to compression. The trachea at this level was slightly narrowed and displaced anteriorly.

Operative Findings and Procedure.—On Jan. 21, 1946, a left thoracotomy was performed under intratracheal, oxygen-ether anesthesia.

After the mediastinal pleura was retracted from the great vessels and the base of the heart, an ascending aorta of normal calibre was seen to leave the heart at its usual site. It passed in front and to the left of the trachea into the posterior mediastinum. Two branches arose from it which were identified as the left common carotid and subclavian arteries (Fig. 8, *A*). Instead of following its usual course down the left thoracic gutter, the aorta curved behind the esophagus and into the right chest. It was obvious that surgical division of the vascular ring could be performed only through a right thoracotomy incision. The wound was closed and the child was returned to the ward pending further surgery through the right side.

A second operation was performed on Feb. 13, 1946, and a right posterolateral thoracotomy incision was made. The pleura was entered through the fifth intercostal space. The apex of the lung was retracted downward and the azygos vein was doubly ligated and divided. The highest intercostal vein was dealt with similarly. This was necessary to obtain adequate exposure of the arteries in question (Fig. 8, *B*).

The most prominent structure first noticed was the aorta emerging from behind the esophagus at a slightly lower level than it was seen to disappear on the left side. It descended down the thorax along the right lateral margin of the vertebral column, curving gently to the left at its distal end so that it went through the diaphragm in the midline. At the angle where the aortic arch became the descending aorta, a large artery came off and ascended to the apex of the thorax. This was an innominate artery which branched into the right common carotid and right subclavian.

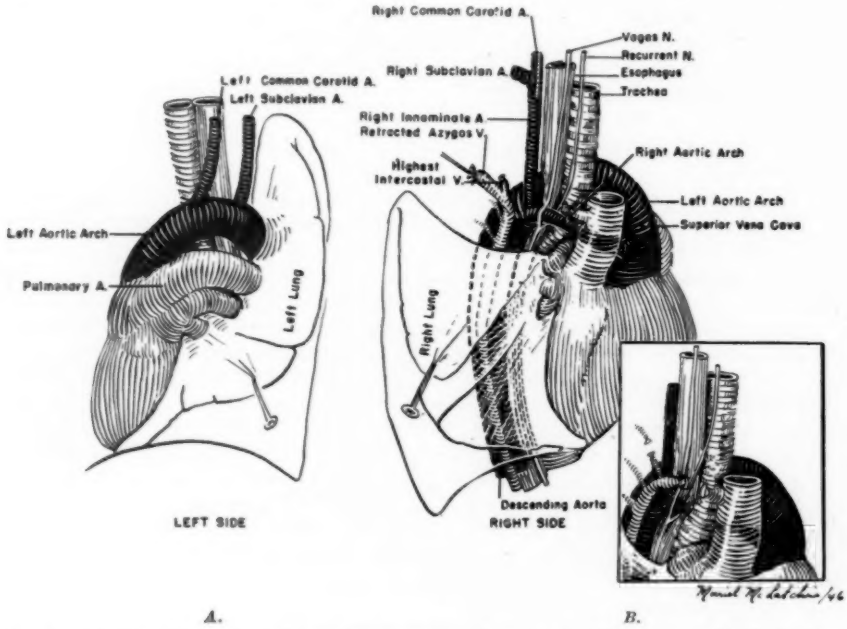


Fig. 8.—Diagram illustrating the anatomy found in Case 2. *A*, View from the left; *B*, view from the right. *Inset:* After division of the right or ventral arch.

As the mediastinal structures were further dissected, a vessel connecting the ascending and descending portions of the aorta came into view. It arose from the ascending aorta just above the base of the heart and traversed the left posterolateral border of the superior vena cava. It then coursed dorsally, slightly superiorly, and to the right, passing over the first portion of the right main bronchus at its origin from the trachea. It joined the descending aorta at the level where the right innominate artery arose. The diameter of this vessel was about one-eighth that of the aorta. There was no doubt that this represented a persistent right fourth aortic arch. A definite groove in the surface of the right main bronchus could be palpated where it passed over and in front of that structure. Since this segment of the vascular ring about the esophagus and trachea was superfluous as a blood conveyer, it was doubly ligated with silk ties and divided. The ligated ends of this vessel separated immediately after division (Fig. 8 *inset*).

No ductus arteriosus or ligamentum was found on the right. The vagus nerve on that side descended in front of the right aortic arch. The left recurrent laryngeal nerve branched from the vagus just caudad to the arch, coursing beneath and behind it to ascend along its usual course. The operation was finished in the routine manner.

Postoperative Course.—Recovery from operation was uneventful save for a tachycardia which persisted for several weeks but gradually subsided.

Embryologic Considerations.—It is interesting to note that the early embryonic arrangement of the aortic arch vessels was apparently a mirror image of the vascular pattern in Case 1. Contrary to Case 1, there was an innominate artery on the right side, and the two surviving vessels on the left became the common carotid and subclavian arteries. The reversal of laterality of these vessels can be appreciated on comparing Figs. 6 and 13, *A*. The evolution of the left aortic arch system was normal except for the failure of the distal half of the sixth arch to appear. As a result, there was neither a patent ductus arteriosus nor ligamentum on that side. This will be more fully discussed below. The left fourth arch became the largest vessel leaving the heart.

The abnormal development of the right arch system led to the ultimate anomalous arrangement of the great vessels. The right ventral aorta between the third and fourth arches disappeared, whereas the segment of the right dorsal aorta between these arches survived (Fig. 13, *A*). The first intersegmental artery connected with this segment and later became the first portion of the right subclavian artery. Because of this disposition of embryonic vessels, an anomalous right innominate artery resulted.

Fig. 9.—Case 2. Chest film showing partial collapse of the right upper lobe and abnormal arrangement of the structures at the base of the heart. Arrow indicates shadow caused by a right-sided descending aorta.

Normally, the right primitive dorsal aorta disappears between the origin of the sixth intersegmental artery and its fusion with the left dorsal aorta (Fig. 5, *A*). In this case, the right dorsal aorta persisted in its entirety (Fig. 13, *A*). Although that portion distal to the right fourth arch remained patent as a vessel, it failed to lengthen with growth of the embryo. With the origin of the right innominate artery acting as a fixed point, the left dorsal aorta was drawn gradually to the right. This vascular shift led to the final placement of the descending aorta on the right. An attempt has been made to show this diagrammatically (Fig. 13, *B* and *C*).

The occurrence described above caused part of the left fourth aortic arch and left dorsal aorta to lie behind the esophagus. The persistent right fourth arch remained to pass in front of the trachea and connect the ascending and descending aortae. A vascular ring about the trachea and esophagus was formed in this manner. Although a ductus arteriosus or its remnants were carefully looked for at both operations, neither was found on the right

or on the left. This would indicate that there was never any connection between the pulmonary and arterial vascular systems via the distal portions of either sixth arch. It seems probable, therefore, that during fetal life there was a shunt between the venous and arterial vascular beds through the interauricular or interventricular septa. The septal defect most likely closed shortly after birth since no characteristic cardiac murmur has ever been heard.

DISCUSSION

Respiratory stridor in infancy is a frequent complaint and may be due to a variety of causes. There is often considerable confusion concerning its etiology. In some cases it is due to an abnormality of the larynx such as a deformity or flaccidity of the epiglottis, arytenoids, or aryepiglottic folds. In these, the onset is usually at birth. Respiratory distress may be absent or quite appreciable. Direct laryngoscopy will establish the diagnosis.

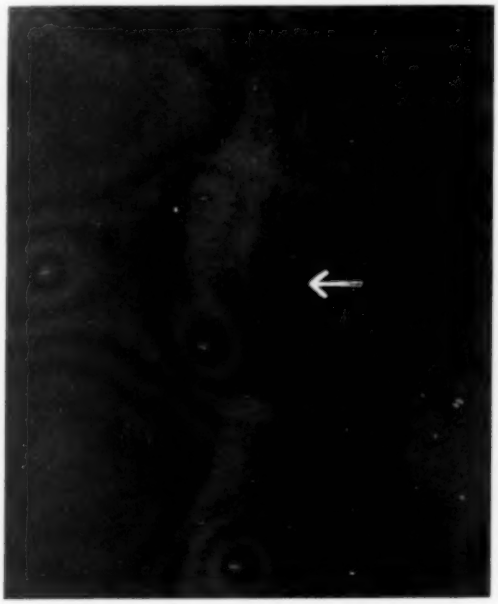


Fig. 10.—Case 2. Posteroanterior view of barium-filled esophagus. Note the reversal of the esophageal deformity as compared with that of Case 1. Arrow points to lateral impression of esophagus by the left aortic arch.

An inspiratory stridor may occur in tetany neonatorum. Usually, there will be other clinical signs. The presence of low serum calcium and elevated serum inorganic phosphorus concentrations with normal serum nonprotein nitrogen and no significant renal insufficiency are characteristic of this diagnosis. Likewise, in idiopathic hypoparathyroidism, these determinations will establish the diagnosis. Laryngeal stridor or crow may also occur in the tetany of healing rickets. In some cases of cerebral damage, stridor is an outstanding sign.

Other causes of inspiratory stridor are the presence of a foreign body in a bronchus, pressure from tuberculosis of the peribronchial lymph nodes, or congenital heart disease. The history, physical examination, x-ray examinations of the chest, and tuberculin tests are helpful in arriving at a diagnosis in such cases.

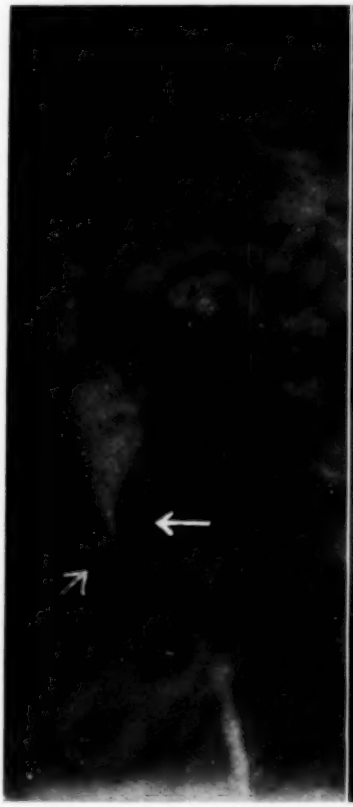


Fig. 11.

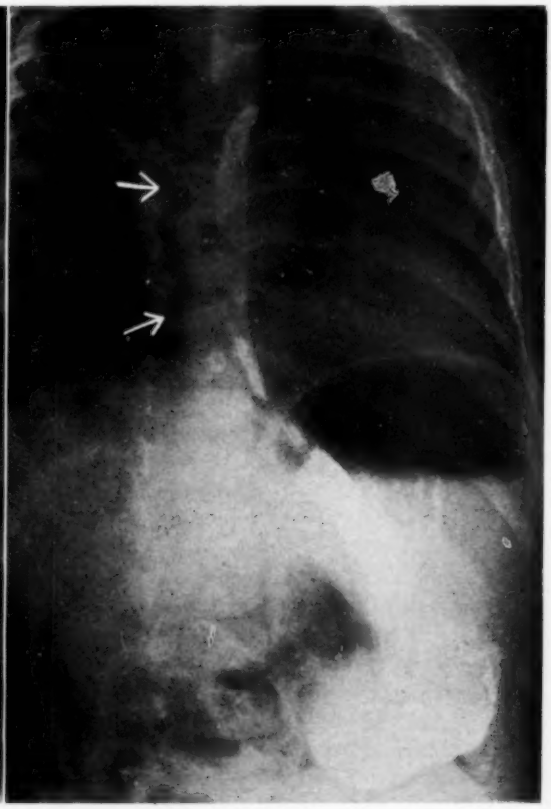


Fig. 12.

Fig. 11.—Case 2. Lateral view of esophagus following a barium swallow. Arrows indicate posterior indentation of esophagus and anterior impression of the trachea.

Fig. 12.—Right anterior oblique view of chest and abdomen to demonstrate the entire barium-filled esophagus with its deformity. Note moderate dilatation of esophagus proximal to the constriction and the descending aorta on the right side. Arrows point to the descending aorta.

Congenital atresia of the posterior choanae, in which the presenting symptoms are a peculiar click on inspiration, marked respiratory difficulty, and cyanosis especially during feeding, may cause stridor. This condition can be diagnosed easily by the detection of obstruction to the passage of a catheter from the nose into the pharynx.

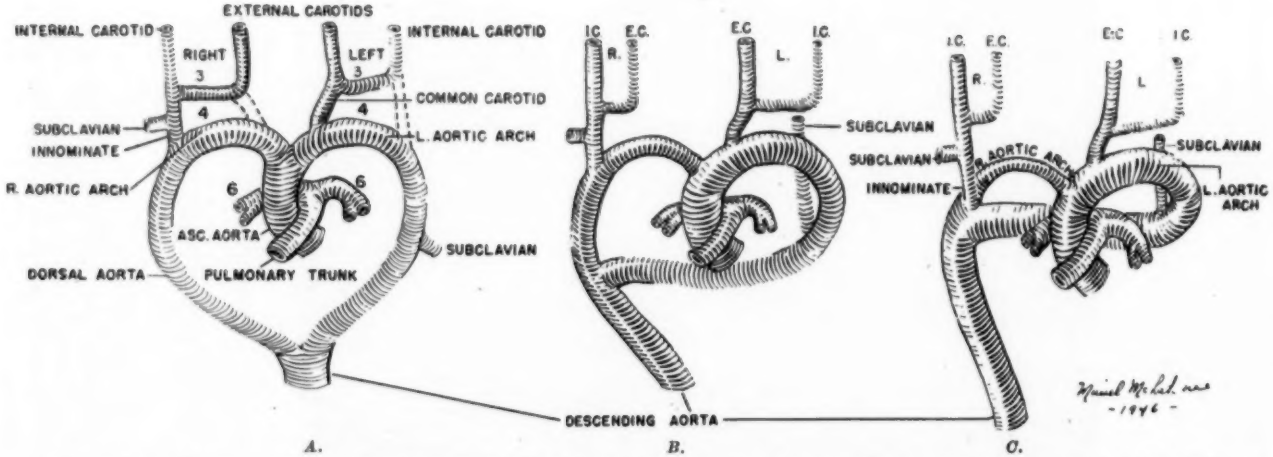


Fig. 13.—*A*, the arrangement of embryonic vessels in Case 2. Note that this is a mirror image of Case 1 except that the distal segments of the sixth arches failed to appear. *B* and *C* show the development of a right descending aorta due to the failure of the persistent right dorsal aorta to lengthen.

In the past, a large number of cases of inspiratory stridor have been attributed to an enlarged thymus. It may be that a large thymus was the cause of respiratory difficulty in a few patients, but it is probable that the thymus was accused wrongly in the majority of cases. A persistent right aortic arch may give the same widening of the upper mediastinum by x-ray as the enlarged thymus. It is possible that some cases of inspiratory stridor which were attributed to an enlarged thymus were really due to an anomalous aortic vascular ring with a large right aortic arch.

In cases where constriction by an anomalous ring composed of a double aortic arch is found, the stridor is usually noticed at birth. Wheezy respiration and attacks of coughing are frequently observed,[11] and the coughing and stridor often become worse when the infant is fed.[14] In many cases it is noted that the infant breathes normally while asleep.

In all cases, the respiratory signs are markedly aggravated by upper respiratory infections.[7, 8] In some instances the respiratory distress is so great as a result of these infections that a tracheotomy has been performed without effect. These children are unusually susceptible to such infections. Repeated pulmonary infections have ultimately led to fatalities in many cases.[17]

As pointed out by Faber and associates,[7] in infants and children with a double aortic arch, noisy breathing appears to be a much more common complaint than dysphagia. Dysphagia is frequently a minor symptom during the first few months while the child is on a liquid diet. As a more solid diet is given, this symptom becomes more pronounced.

Associated cardiac anomalies occur[2] comparatively rarely. Usually, these infants do not have other congenital abnormalities.[16]

Diagnosis of Double Aortic Arch.—The observation of respiratory wheezing or stridor even without dysphagia which is aggravated by deglutition should make one suspect the presence of a double aortic arch.

A plain posteroanterior roentgenogram of the chest may arouse suspicion of anomalous great vessels about the heart because of a widened mediastinal shadow extending mostly to the right. Often the normal aortic knob is not seen on the left. Left and right oblique views may show the aorta ascending on the right and passing behind the esophagus respectively.[2]

The most informative special examination is that of the esophagus following the ingestion of barium. The lateral surface of this structure is indented by the aortic arch which carries the major blood load. The defect can occur on either side as illustrated by Figs. 2 and 10. In Case 1, the largest fourth aortic arch and the lateral esophageal indentation on the right. The converse was true in Case 2. A similar defect is also seen posteriorly at the site of the retroesophageal aorta.

Sometimes there may be forward and lateral displacement of the trachea and esophagus. They have been noted to be displaced to the left by right aortic arches.[2] Gross[8] and Neuhauser[12] point out that narrowing of the trachea at the site of the constricting vascular ring is a prominent feature. This is best illustrated by bronchography, although it may be seen adequately with plain chest

films. If the above tracheal and esophageal deformities are noted, esophagoscopy is an unwise procedure, because of the danger of perforation.

Surgical Approach.—It is most important for the surgeon to know which side of the chest he should enter to correct this lesion. A study of previously reported cases suggests that a left chest approach is the wisest in most instances.[3] This is because the surviving left fourth arch is usually more amenable to division, since the right aortic arch almost always conveys most of the arterial blood. The development of the aortic arch system, however, is so complex that it is potentially subject to many variations. As more of these anomalies are studied, hitherto unreported vascular arrangements probably will be brought to light. The surgeon must, therefore, be careful to choose the correct side of the chest through which to operate.

The cases presented here may be helpful in selecting the accurate surgical approach. If the posterior and right lateral aspects of the esophagus are indented by the larger persistent right aortic arch (Fig. 2), the lesser aortic arch, which is the vessel to be divided, will be found on the left anterolateral aspect of the mediastinum. The visualization of the main aorta descending down the left side of the vertebral column (Fig. 4) would corroborate this probability. Obviously, under these conditions, the vessel to be chosen for ligation will be best reached through the left pleural cavity. Case 1 illustrates this combination of x-ray findings. As previously emphasized, Case 2 is a mirror image of Case 1. Here there were defects of the left lateral and posterior surfaces of the esophagus (Figs. 10 and 11) caused by the larger left aortic arch. The descending aorta was seen by x-ray in the right chest (Fig. 12). As stated in the operative report of Case 2, the anomalous, smaller, right arch could be reached only through the right chest. In summary, when an annular double aortic arch about the trachea and esophagus is suspected, the lateral esophageal deformity and the location of the descending aorta should be helpful findings in deciding which pleural cavity is to be entered.

Conclusion.—Patients with symptoms caused by this congenital anomaly should be operated upon. It is true that this lesion has been found at autopsy in elderly individuals who have never had dysphagia or respiratory distress.[3, 6] As Blackford and associates[4] point out, however, it is conceivable that arteriosclerotic or hypertensive changes in later life may initiate a symptom complex. One should, therefore, consider the desirability of operation early in life even in the absence of symptoms.

Grateful acknowledgment is made to Dr. John L. Bremer for his invaluable assistance with the embryologic aspects of these cases and to Dr. Laurence L. Robbins for his interpretations of the roentgenologic studies in each.

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PENICILLIN IN TREATMENT OF DIPHTHERIA AND DIPHTHERIA CARRIERS

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FLEMING,[1] in 1929 and in 1932,[2] and subsequently Chain and associates,[3] demonstrated that penicillin inhibited the growth of *Corynebacterium diphtheriae* in vitro. These observations, plus the successful inhibition of the growth of *C. diphtheriae* in infected guinea pigs,[4] suggested the clinical application of penicillin to the treatment of both persons acutely ill with diphtheria and convalescent carriers. The results were very encouraging in the treatment of the first group, five convalescent carriers and six patients with faucial diphtheria.[5] However, this limited experience left many questions unanswered. It was necessary to determine the most suitable dosage and route of administration, the duration of treatment, its effect on complications due to diphtheria toxin and secondary invaders, and, above all, whether or not penicillin was regularly effective and to what extent it could be relied upon.

The presence of diphtheria among prisoners of war and among American soldiers in one of the base sectors of the European Theater of Operations in the autumn and winter of 1944 afforded the opportunity to investigate these problems. The study was undertaken simultaneously in five hospitals. The data here reported are the composite results of observations made in the hospitals concerned.

OUTLINE OF STUDY

1. It was stressed that penicillin is not a substitute for antitoxin and should not be used as such. This was based upon previous laboratory observations.

2. All patients suspected of having diphtheria were to receive 40,000 units of antitoxin intramuscularly. If indicated clinically, an additional 20,000 units might be given intravenously and larger doses of antitoxin might be given if considered necessary.

3. All patients with diphtheria, except those seen at the Two Hundred Thirty-Fifth General Hospital, were to have penicillin, to be begun after a throat culture was taken but without waiting for the laboratory report.

The penicillin dosage and manner of administration suggested were as follows:

Forty-Third General Hospital.—20,000 units intramuscularly every three hours.

Prisoner of War Hospital (8277).—20,000 units intramuscularly every two hours.

Prisoner of War Hospital (8276).—Spraying of nose and throat every hour during the day and every three hours at night with penicillin solution (1,000 units per milliliter of physiological sodium chloride solution).

Third General Hospital.—20,000 units intramuscularly every three hours, plus spraying of the nose and throat every hour for the first day and every three hours thereafter day and night.

Two Hundred Thirty-Fifth General Hospital.—The patients were to receive antitoxin and to serve as controls.

4. Patients were to receive penicillin until three, daily, consecutive, throat cultures were negative. Thereafter, cultures were to be taken daily for three days, every second day for six days, and every third day for nine days. If all of these were negative, the patient was to be considered free of *C. diphtheriae*.

5. The virulence and type of the bacteria isolated from each patient were to be determined.

METHODS AND MATERIALS

Direct smears of the throat or other lesions were made on admission. At the same time, swabs with material from the diseased areas were inoculated on Loeffler's serum agar and incubated for from eighteen to twenty-four hours. Suspicious organisms found on the direct smear were reported as such, but a definite diagnosis of diphtheria was not made at this time. Patients with typical lesions containing organisms morphologically similar to *C. diphtheriae* were treated with antitoxin. After eighteen to twenty-four hours, all Loeffler cultures were smeared on glass slides, stained with alkaline methylene blue or Neisser's stain, and examined. Frequently, a positive diagnosis could be made from this original culture. Occasionally, however, the morphologically typical beaded and banded rods were absent and it was necessary to subculture before a positive diagnosis could be made. All Loeffler cultures were streaked onto tellurite chocolate agar and blood agar plates. From the latter, concomitant beta hemolytic streptococcus infection could be determined. Typical colonies of *C. diphtheriae*, appearing as dull, somewhat rounded, gray-black, butyraceous colonies and consisting of gram-positive rods, were picked and subcultured on Loeffler's serum agar. After twenty-four hours of incubation these cultures were again examined and if morphologically characteristic of *C. diphtheriae* they were transplanted to three, semisolid, tryptose phosphate agar media containing dextrose, sucrose, and dextrin, respectively. This semisolid agar maintained as good a growth of *C. diphtheriae* as the common Hiss serum water which was likewise used toward the latter part of the experiment and was easier to prepare. All sucrose fermenters were discarded and reported as diphtheroids. It was found that all *C. diphtheriae* fermented dextrose and dextrin in from twenty-four to forty-eight hours, and a positive diagnosis of *C. diphtheriae* could be and was made at this time.

Because of the scarcity of animals, cultures were accumulated until at least six to ten were available and the pure Loeffler cultures were subcultured on tryptose agar. After eighteen hours the growth was washed down with sterile saline, the mixture diluted to a nephelometer reading of 3, and this mixture used for the virulence tests. Either rabbits or guinea pigs were used. The method used was as follows: The dorsum of the animal was shaved the day before the test. The shaved area was marked off into blocks with indelible pencil, each

block containing 0.1 c.c. of the nephelometer culture mixture. As many as ten virulence tests could be done on one animal. Five hours after the initial injections, the animal received 1,000 units of diphtheria antitoxin intravenously. One-half hour later, 0.1 c.c. of the culture-saline mixture, kept in the refrigerator since its preparation, was injected on the opposite shaved site of the animals to serve as controls. In from three to five days these virulence tests were read. All virulent cultures resulted in necrosis of the area of injection. Nonvirulent organisms caused only a slight redness for twenty-four to forty-eight hours, which rapidly disappeared. All cultures of the throat yielding *C. diphtheriae* gave positive virulence tests.

Identification of the type of strain of *C. diphtheriae* was not attempted at the time. Subsequent examinations of all available stock cultures revealed that all but two, which were of a gravis strain, belonged to the mitis type of *C. diphtheriae*. Virulence tests were performed on all strains isolated from patients at the Third General Hospital and in about 50 per cent of the cases from other hospitals concerned. Cases with avirulent strains were excluded from this survey.

The prevailing wartime conditions prevented close adherence to the program outlined in some hospitals. At the Two Hundred Thirty-Fifth General Hospital, because of the need for ward space, the control patients who remained carriers for thirty days were treated with penicillin. Twenty persons with faucial diphtheria admitted thereafter were treated with intramuscular penicillin. Transfer of patients interrupted the continuity of the observations. Transfer of personnel concerned with the investigation interferred with the case records and limited the amount of laboratory work.

Thus the original plan was modified to comply with existing conditions. Nevertheless, eighty patients with faucial diphtheria were carefully observed and will serve for the evaluation of the efficacy of penicillin in diphtheria. Forty-two patients with faucial diphtheria were treated with antitoxin alone and served as controls, and thirty-five convalescent carriers were treated with penicillin administered intramuscularly locally, or both ways.

RESULTS

Faucial Diphtheria.—

Local Penicillin: Penicillin in the form of a nose and throat spray of 1,000 units per milliliter of physiologic saline solution was administered every hour during the day and every three hours at night for seven days to twenty-one patients. Only two of the twenty-one patients became negative for *C. diphtheriae* within that period.

Intramuscular Penicillin: Comparison of results of the eighty penicillin treated patients with the control group (see Figs. 1 and 2 and Tables I and II) reveals that at five days after onset of the disease the percentage of positive throat cultures among the penicillin treated patients was 27.5 per cent, 100 per cent for forty-two controls, and 83 per cent for the 457 reported by Hartley and Martin[6]; at ten days, positive cultures were obtained from 7.5 per cent, 92.8

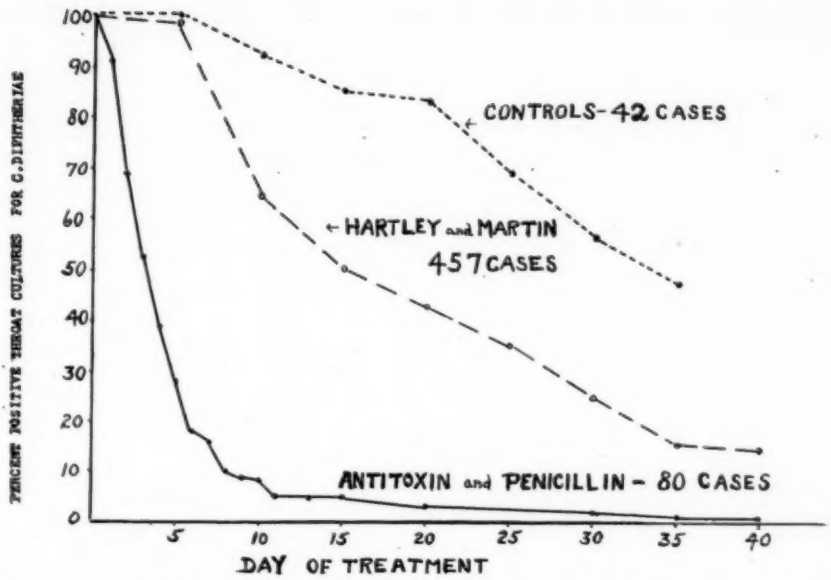

Fig. 1.—Comparison of the results obtained in the treatment of diphtheria with antitoxin alone and with penicillin plus antitoxin.

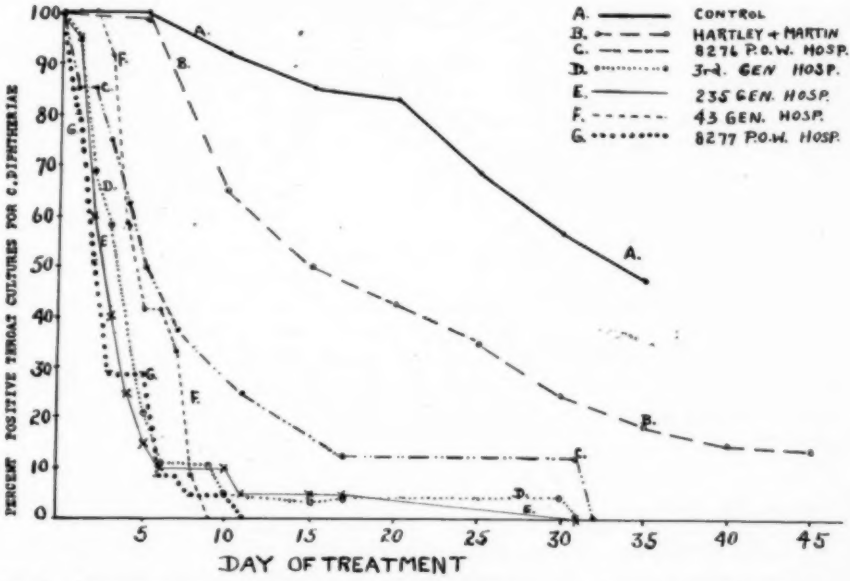

Fig. 2.—Comparison of the results obtained in the treatment of diphtheria with antitoxin alone and with penicillin plus antitoxin in each of the five hospitals.

TABLE I. DURATION OF POSITIVE NOSE AND THROAT CULTURES FOR *C. Diphtheriae* IN CASES OF FAUCIAL DIPHTHERIA TREATED WITH PENICILLIN AND ANTITOXIN AT THE VARIOUS HOSPITALS

	POSITIVE CULTURES IN EACH HOSPITAL										TOTAL POSITIVE CULTURES (80 CASES)	
	43 G.H. (12 CASES)		235 G.H. (20 CASES)		3 G.H. (19 CASES)		8276 P.O.W. (8 CASES)		8277 P.O.W. (21 CASES)			
DAYS	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	12	100	19	95	18	94.7	7	87.5	17	80.9	73	91.25
2	12	100	12	60	13	68.4	7	87.5	11	52.4	55	68.75
3	11	91.6	8	40	11	57.9	6	75	6	28.6	42	52.50
4	7	58.3	5	25	8	42.1	5	62.5	6	28.6	38	38.75
5	5	41.6	3	15	4	21.0	4	50.0	6	28.6	22	27.50
6	5	41.6	2	10	2	10.5	3	37.5	2	9.5	14	17.50
7	4	33.3	2	10	2	10.5	3	37.5	2	9.5	13	16.25
8	1	8.3	2	10	2	10.5	2	25.0	1	4.8	8	10.00
9	0	0	2	10	2	10.5	2	25.0	1	4.8	7	8.75
10			2	10	1	5.2	2	25.0	1	4.8	6	7.50
11			1	5	1	5.2	2	25.0	0	0	4	5.00
17			1	5	1	5.2	1	12.5			3	3.25
31			0	0	0	0	1	12.5			2	2.5
32							1	12.5			2	2.5
77							0	0			0	0

TABLE II. RATE OF DISAPPEARANCE OF *C. Diphtheriae* IN PATIENTS TREATED WITH ANTITOXIN AND WITHOUT PENICILLIN (42 CASES)

	PATIENTS WITH POSITIVE NOSE OR THROAT CULTURE						
	3 G. H.		235 G. H.		TOTAL		HARTLEY AND MARTIN (457 CASES)
DAYS	NO.	%	NO.	%	NO.	%	%
5	18	100	24	100	42	100	100
10	18	100	21	87.5	39	92.8	65
15	17	94.4	19	79.1	36	85.7	50
20	17	94.4	18	75	35	83.3	43
25	15	83.3	14	58.3	29	69.0	35
30	14	77.7	10	41.6	24	57.1	25
35	12	66.6	8*	33.3	20	47.6	18
40	10	55.5					15
45	9	50.0					
50	9	50.0					8
55	8	44.4					
60	5	27.7					7
65	4	22.2					
over 65	2*	11.1					6

*Treated with penicillin as a convalescent carrier.

per cent, and 65 per cent respectively. At fifteen days, less than 5 per cent of the penicillin treated patients remained positive, against 85.7 per cent for our controls and 50 per cent for the patients reported by Hartley and Martin.[6] Thus penicillin affected a considerable reduction in the period of infection with *C. Diphtheriae*. The results were similar in each of the five hospitals.

Treatment of Carrier State.—

Local Penicillin: At the Two Hundred Thirty-Fifth General Hospital, eight patients who were convalescent carriers for from twenty-six to thirty days were given penicillin nose drops every three hours for seven days. All ceased to be carriers within seven days.

In another hospital where the patients had been carriers for a longer time and had previously been treated with intramuscular penicillin, only two of thirteen were cleared of *C. diphtheriae* during the seven- to twenty-three-day period of local therapy.

Intramuscular Penicillin: Intramuscular penicillin, 20,000 units every three hours, terminated the carrier state within four days in six of the nine patients at Prisoner of War Hospital (8277), and with 15,000 to 20,000 units every three hours, four of five carriers treated at the third General Hospital became negative. Thus ten of fourteen carriers were cured with penicillin.

PENICILLIN TREATMENT OF CONVALESCENT CARRIERS OF *C. Diphtheriae*

Local Penicillin.—

Two Hundred Thirty-Fifth General Hospital: Eight patients, convalescent carriers for from twenty-six to thirty days prior to treatment, received nose drops of penicillin* saline solution every hour during the day and every three hours at night.

2 became negative 1 day after treatment was started
1 became negative 2 days after treatment was started
4 became negative 5 days after treatment was started
1 became negative 6 days after treatment was started

Prisoner of War Hospital (8277): Thirteen convalescent carriers,† some previously treated with penicillin unsuccessfully, received nose and throat spray of penicillin* for from seven to twenty-three days.

1 became negative 7 days after treatment was started
1 became negative 11 days after treatment was started
11 remained carriers after treatment was discontinued.

Intramuscular Penicillin.—

Prisoner of War Hospital (8277): Nine convalescent carriers† received intramuscular penicillin 20,000 units every 3 hours. The average total amount injected was 1,540,000 units.

4 became negative 3 days after treatment was started
2 became negative 4 days after treatment was started
2 became negative 12 days after treatment was started
1 failed to respond to a total of 2 million units given in 12.5 days.

Third General Hospital: Five cases were treated with intramuscular penicillin, 15,000 to 20,000 units every three hours.

3 became negative 1 day after treatment was started
1 became negative 2 days after treatment was started, but recurred and was cleared by nasal spray
1 became negative 1 day after treatment was started, became positive again after 5 days, became negative after 740,000 units were given in 6 days then again became positive

Effect of Penicillin on Course of Diphtheria and On Complications.—

The diphtheritic membrane persisted for about the same length of time in the treated patients as in the controls. The faucial edema and the subjective feeling of soreness of the throat were, however, favorably influenced by penicillin.

*A solution of 1,000 units of penicillin per milliliter of physiologic saline was used for nose drops and nasal spray.

†All patients had been carriers for at least thirty days prior to treatment with penicillin.

Although statistical data are not available, it was our impression that there was an appreciable clinical difference between the penicillin treated patients and the controls in the incidence and severity of complications due to pyogenic organisms. In the group treated with antitoxin alone, cervical adenitis was more commonly observed and persisted longer. Several patients with diphtheria had large peritonsillar swellings. These responded to penicillin. Three of these were suspected of being abscessed, but pus was not obtaind on incision. These too cleared on penicillin therapy. Otitis media and clinical sinusitis likewise occurred among the controls but did not develop in the patients treated with penicillin. These conditions, if present on admission to the hospital, responded to penicillin therapy.

TABLE III. TOXIC COMPLICATIONS

CASE	SEVERITY OF DIPHTHERIA	ANTITOXIN		COMPLICATIONS	
		DOSAGE (UNITS)	DAY ADMINISTERED	TIME OF APPEARANCE AFTER ANTITOXIN GIVEN	DESCRIPTION
Forty-Two Cases Treated With Diphtheria Antitoxin and No Penicillin					
1	Severe	40,000	5th	27 days	Palatal paralysis
				41 days	Myocarditis with bundle branch block
				58 days	Paralysis respiratory muscles including diaphragm; died 58th day
2	Moderate	40,000	2nd	41 days	Polyneuritis
Forty Cases Treated With Penicillin and Diphtheria Antitoxin					
Penicillin 25,000 units every three hours					
3	Severe	150,000	5th	4th week	Palatal pareses; myocarditis, moderate
4	Severe	80,000	4th	25th day	Myocarditis; moderate
				4th week	paresis, palate right side
5	Severe	100,000	5th	3rd week	Palatal paresis, transient; more marked 6th week
				24th day	Myocarditis, mild
Penicillin 20,000 units every two hours					
6	Moderate	40,000	1st	4th week	Paralysis of accommodation
7	Severe	100,000	8th	18th day	Palatal paralysis
8	Severe	60,000	6th	32nd day	Palatal paralysis
9	Severe	60,000	2nd	22nd day	Palatal paralysis

Toxic neurological and cardiac complications were observed in two of the forty-two control patients and in seven of the eighty treated with penicillin intramuscularly. Data on the twenty-one patients treated with penicillin spray are not available. Most of the neurological complications occurred in patients who came to the hospital between the third and eighth day of the disease, although there were a few such complications among those who were presumably admitted on the first or second day of their illness.

There were no deaths among the patients treated with penicillin and only one among the controls.

Special mention must be made of three patients who developed complications after intensive serum and penicillin therapy. In each the diphtheria was severe and the patients were admitted on the fourth, fifth, and sixth days of the disease. Because of the widespread membranes, the toxemia, and the severe cervical adenitis, large doses of antitoxin, 80,000, 100,000, and 150,000 units were administered, and penicillin was started immediately. In one instance, 40,000 units of penicillin were injected every three hours for the first three days, and 25,000 units every three hours thereafter. In the other two, 25,000 units were injected intramuscularly every three hours. In addition, penicillin was sprayed in the nose and throat every hour during the first day and every three hours thereafter. Even though these patients received intensive therapy and improved rapidly, each subsequently developed palatal paralysis and cardiac changes, and one developed peripheral neuritis. Once more these cases demonstrate the fact that penicillin is not a substitute for antitoxin.

Of a total of 157 patients with diphtheria, tonsils were present in 147, or 93.63 per cent. Of the carriers, thirty-five of forty-two, or 83.33 per cent, had tonsils. The tonsils were generally large, cryptic, irregular, and in many cases scarred. There seemed to be a clinical correlation between the persistence of the carrier state and the character of the tonsillar tissue present, but statistical data were not obtained. The patients most difficult to clear of *C. diphtheriae* were those whose tonsils were very large and cryptic. In one carrier in whom penicillin failed to eradicate the infection, tonsillectomy was successful. The tonsils of this patient on section yielded a pure culture of *C. diphtheriae*.

DISCUSSION

Ercoli and associates,[7] demonstrated that penicillin exerted a striking antibacterial effect on the bacteriemia produced in mice by the intraabdominal injection of a suspension of *C. diphtheriae* in mucin. They found penicillin to be ineffective in the toxemic infection of guinea pigs although it presumably prolonged the survival time by delaying the growth of the diphtheria bacilli. They suggested that, under the practical conditions of diphtheria in human beings, penicillin may be useful for its antibacterial effect, e.g., prophylaxis of exposed contacts, very early cases, and carriers; but they emphasized the importance of antitoxic treatment of active cases. Skinner[8] reported the favorable bacteriostatic effect of penicillin in the treatment of diphtheria patients and carriers. With a dosage of 100,000 units daily, eleven of fifteen patients were rendered free of *C. diphtheriae*, although smaller doses were less effective. Thrift[9] reported upon the favorable effect of penicillin used topically in clearing a persistent nasal carrier of *C. diphtheriae*.

These reports added to our data seem ample evidence that penicillin is an effective agent in the treatment of diphtheria, yet we were not invariably successful. With a dosage of 20,000 units every three hours injected intramuscularly, 7.5 per cent of our patients remained positive for *C. diphtheriae* after ten days of therapy. In one of the hospitals servicing prisoners of war, forty-six patients with diphtheria not included in our data had been treated

with penicillin. Some of these had had 20,000 units of penicillin every three hours intramuscularly for three or five consecutive days or a total of 480,000 and 800,000 units. Throat cultures taken fourteen days after the treatment was started were positive for more than 25 per cent of the patients, indicating that these dosages were inadequate or that the penicillin had not been continued long enough.

The dosage of penicillin administered to forty of our eighty patients with faucial diphtheria and to nine carriers was 20,000 units every three hours intramuscularly. The deviations from this dosage for patients with faucial diphtheria were 20,000 units every two hours for twenty-one patients, 25,000 units every three hours for six patients and 20,000 units every three hours accompanied by simultaneous spraying of the nose and throat with a saline solution of 1,000 units of penicillin per milliliter in thirteen cases.

The results in all groups were too similar (Fig. 2) and the groups too small to warrant conclusion as to which dosage was more effective. All dosages seemed adequate for most of the patients, provided that the penicillin was continued until three, consecutive, daily, negative cultures were obtained, and provided that penicillin was reinstituted immediately after the nose or throat culture reverted to positive. In such cases, penicillin was again administered until three consecutive daily negative cultures were obtained. Few patient's cultures became positive again after the second course of penicillin therapy.

Between 420,000 and 2,400,000 units of penicillin were needed to render the acute cases of faucial diphtheria negative. For convalescent carriers the total dose needed was generally less, although it necessitated up to 2,000,000 units in some instances.

It has been demonstrated by Ercoli[7] that a concentration of 1.25 to 1.5 units per milliliter, as measured by the cup test against *Staphylococcus aureus* number 20, completely inhibited the growth of stock strains of *C. diphtheriae*, while partial inhibition could be obtained in dilution of 0.35 unit per milliliter. This represents about 100 times the concentration effective against streptococci and pneumococci. Buxbaum and associates[10] found that over 50 per cent of 348 strains of *C. diphtheriae* were inhibited by a concentration of penicillin of 0.25 to 0.50 unit per milliliter, more than two thirds of the strains responded to 1 unit per milliliter, but some strains required 1.50, 2.0, and 4.0 units per milliliter, while few strains required 10 units for complete inhibition. Thus, larger doses of penicillin than have been used heretofore may be indicated for some of the strains. To attain a blood concentration of penicillin more than 1.0 unit per milliliter or high enough for most of the strains, 30,000 to 40,000 units should be injected intramuscularly every three hours.

The continuation of penicillin until three, consecutive, daily, negative, pharyngeal cultures were obtained seemed satisfactory, but there were recurrences of positive cultures in some of these cases within one to five days after penicillin was stopped. Penicillin immediately reinstituted in these cases and continued as in the first course of therapy was effective with rare exception. If, however, the second course of therapy was delayed for ten to fourteen days or longer, the results seemed less favorable. It was our impression that if a

third or fourth course of penicillin became necessary it became increasingly difficult to clear the patient of the infection. This raised the possibility that the particular strains of *C. diphtheriae* involved had acquired greater resistance to penicillin. Unfortunately, due to limited facilities, we were not able to decide this question at that time.

The criterion established for cure, nine, consecutive, negative, throat cultures within a period of eighteen days, was rigid. Had we accepted the usual three negative cultures on alternate days, some of the more stubborn infections would have been missed. More carriers would have been discharged, and the data for the efficacy of penicillin might have appeared better. Three or more negative cultures over a period of ten days would suffice, we believe, to eliminate most of the persistent carriers.

The data presented show definitely that in acute faucial diphtheria intramuscular penicillin was usually successful in eradicating the infection, whereas local therapy in form of a nose and throat spray of 1,000 units per milliliter failed in nineteen of twenty-one cases. In the convalescent carriers, local therapy seemed more successful in one hospital than in another. The results with local penicillin in the carriers are not convincing but are sufficiently encouraging to warrant further trial.

It has been suggested that penicillin be used prophylactically for susceptible exposed individuals. This procedure we believe must await much confirmatory data on the clinical effect of penicillin and a simpler procedure than repeated, three-hour, intramuscular injections of penicillin.

Penicillin has been recommended as a substitute for antitoxin in patients hypersensitive to horse serum. The incidence of complications among penicillin treated cases suggest that the withholding of antitoxin might prove to be a dangerous procedure. It would be justified if it were impossible to desensitize the patient for horse serum and if the possible harm anticipated from the antitoxic serum in a particular case were considered greater than that which might result from the effect of diphtheria toxin. Such cases are rare.

CONCLUSIONS

1. Patients with faucial diphtheria treated with antitoxin and penicillin, the latter injected intramuscularly every three hours until three, consecutive, daily, negative, nose and throat cultures were obtained, were rendered diphtheria negative more rapidly than were the patients who received antitoxin and no penicillin.

2. Carriers of virulent *C. diphtheriae* were likewise rendered free of the bacteria by treatment with penicillin.

3. Penicillin applied locally in the form of nose drops or as nasal spray was not effective in faucial diphtheria, but seemed more promising in the treatment of carriers.

4. Penicillin was ineffective in preventing toxic complications of diphtheria, but seemed to hasten the clearing and further the development of complications due to pyogenic organisms.

5. Penicillin should not be used as a substitute for diphtheria antitoxin.

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STUDIES ON PERTUSSIS IMMUNIZATION

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I. *Immunization of Young Infants With Alum-Precipitated Pertussis Vaccine.*—As reported in a previous publication,[1] it was found that 75 per cent of infants below the age of 6 months developed agglutinins as a result of immunization with alum-precipitated pertussis vaccine. Young infants tolerated the vaccine extremely well, local reactions occurring in only 8.6 per cent and systemic reactions in 7.1 per cent. A follow-up study subsequent to immunization revealed that the incidence and severity of pertussis in those followed who had known exposure, familial or casual, were much less than in a similar group of nonimmunized urban clinic patients.

II. *Effect of Age on Agglutinin Response to Pertussis Immunization.*—The recommended three doses of alum-precipitated pertussis vaccine (40 billion per cubic centimeter, Lilly) were administered at monthly intervals to 8,690 Negro children from 2 weeks to 5 years of age. The agglutinin titers were run by the method of Miller and Silverberg[2] approximately two to four months following completion of immunization. The children were unselected except for the fact that their agglutinin titers were all negative prior to immunization.

The results show that infants below the age of 3 months developed agglutinins just as well as any age group (Tables I and II and Figs. 1 and 2). The total positive agglutination titers in infants below 3 months of age (92.10 per cent was comparable to the 3- to 6-month age group and the 6- to 12-month group (94.39 per cent and 93.99 per cent respectively). Similarly, the strongly positive reactions in the 2-week to 3-month group (51.44 per cent) were as good as in any age group except the 18- to 24-month group, in which for some reason a large number developed high titers (67.59 per cent).

Some investigators[3] have found that young infants develop antibodies very poorly in response to pertussis vaccine. However, quantitative methods used by the earlier workers were ill adapted for the accurate assay of the antibodies concerned. Employment of a more adequate technique has resulted in many cases in the demonstration of antibodies. There is reason to believe, as will be shown later, that alum-precipitated pertussis vaccine is superior to fluid vaccine in the immunization of young infants. It has been repeatedly observed that some individuals do not have, or have a very poor capacity to produce antibodies. This has been attributed to inferior "antibody factories." This property, however, is not correlated with age as regards pertussis immunization, provided an appropriate vaccine is used. The capacity to produce pertussis antibodies is present in the young infant as in any other individual; the facility with which the antibodies are exfoliated into the blood stream of the infant may require a more prolonged antigenic stimulus such as is afforded by the alum-precipitated vaccine.

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TABLE I. EFFECT OF AGE ON AGGLUTININ RESPONSE TO PERTUSSIS IMMUNIZATION WITH ALUM-PRECIPITATED VACCINE

AGE GROUP	AGGLUTINATION TITERS																			
	0	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	TOTAL	0	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560
	Number Titers											*Per Cent Titers*									
2 wk.-3 mo.	189	89	173	130	294	287	763	377	52	39	2,393	7.90	3.72	7.23	5.43	12.29	11.99	31.89	15.75	2.17	1.63
3-6 mo.	122	52	87	248	261	411	472	324	111	87	2,175	5.61	2.39	4.00	11.40	12.00	18.90	21.70	14.90	5.10	4.00
6-12 mo.	65	41	39	107	145	106	314	198	53	13	1,081	6.01	3.80	3.61	9.90	13.41	9.80	29.05	18.32	4.90	1.20
12-18 mo.	57	75	131	53	44	141	219	131	35	22	908	6.28	8.26	14.43	5.84	4.84	15.53	24.12	14.43	3.85	2.42
18-24 mo.	42	22	35	33	66	60	156	296	39	17	786	5.28	2.76	4.60	4.14	8.29	7.54	19.60	37.18	8.67	2.14
2-3 yr.	20	9	62	67	51	173	181	120	29	15	727	2.75	1.24	8.53	9.21	7.01	23.80	24.90	16.51	3.99	2.06
3-5 yr.	22	7	111	57	83	53	45	178	30	24	610	3.61	1.14	18.20	9.34	13.61	8.69	7.38	29.18	4.92	3.93

TABLE II. EFFECT OF AGE ON DEGREE OF AGGLUTININ RESPONSE TO PERTUSSIS IMMUNIZATION WITH ALUM-PRECIPITATED VACCINE

AGE GROUP	AGGLUTINATION TITERS							
	TOTAL POSITIVE		SLIGHTLY POSITIVE (1:10 TO 1:40)		STRONGLY POSITIVE (1:320 TO 1:2,560)		MODERATELY POSITIVE (1:80 TO 1:160)	
	NO.	%	NO.	%	NO.	%	NO.	%
2 wk. to 3 mo.	2,204	92.10	392	16.38	581	24.28	1,231	51.44
3 to 6 mo.	2,053	94.39	387	17.79	672	30.90	994	45.70
6 to 12 mo.	1,016	93.99	187	17.31	251	23.21	578	53.47
12 to 18 mo.	851	93.72	259	28.53	185	20.37	407	44.82
18 to 21 mo.	754	94.72	90	11.30	126	15.83	538	67.59
2 to 3 yr.	707	97.25	138	18.98	224	30.81	345	47.46
3 to 5 yr.	588	97.39	175	28.68	136	22.30	277	45.41

III. *Comparative Value of the Type of Pertussis Vaccine on Agglutinin Response of Young Infants.*—Fluid, alum-precipitated, and combined vaccines were administered to 5,028 Negro infants below the age of 3 months, according to the schedule in Table III.

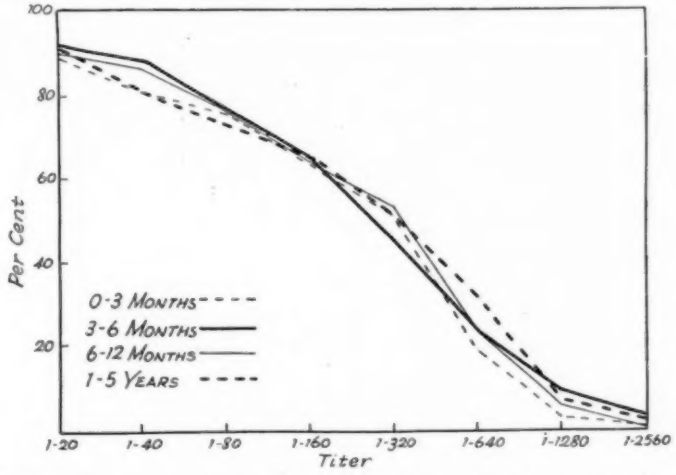

Fig. 1.—The effect of age on the agglutinin response to pertussis immunization with alum-precipitated vaccine.

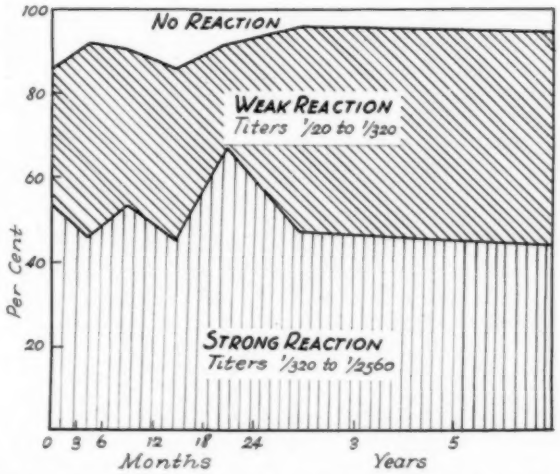

Fig. 2.—The effect of age on the degree of agglutinin response to pertussis immunization with alum-precipitated vaccine.

The results (Table IV) show conclusively that the fluid vaccines are definitely inferior in agglutinin production to alum-precipitated pertussis vaccine in the immunization of very young infants. The fluid vaccines (*A* and *B*)

TABLE III. SCHEDULE OF PERTUSSIS IMMUNIZATIONS WITH VARIOUS TYPES OF VACCINES

AGE	TYPE OF VACCINE AND DOSE				
	FLUID VACCINE		ALUM-PRECIPITATED VACCINE	PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (ANHYDROX)	
	TYPE A (20 BILLION PER C.C.)	TYPE B (40 BILLION PER C.C.)	TYPE C (40 BILLION PER C.C.)	TYPE D (20 BILLION PER C.C.)	TYPE E (MIXED)
1-2 mo. (first dose)	1 c.c.	0.5 c.c.	0.2 c.c.	0.5 c.c.	1.0 c.c. vaccine D
2-3 mo. (second dose)	2 c.c.	1.0 c.c.	0.3 c.c.	1.0 c.c.	1.0 c.c. vaccine B
3-4 mo. (third dose)	2 c.c.	1.0 c.c.	0.5 c.c.	1.0 c.c.	1.0 c.c. vaccine D
Total dose	100 billion	100 billion	40 billion	50 billion	80 billion

TABLE IV. THE COMPARATIVE VALUE OF THE TYPE OF PERTUSSIS VACCINE IN THE AGGLUTININ RESPONSE OF YOUNG INFANTS

TYPE OF VACCINE		AGGLUTINATION TITERS																				
		0	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	TOTAL	0	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560
		Number Titers											*Per Cent Titers*									
Fluid	A	91	43	306 91	172	179 109	70	146 88	32	19	7	722	12.60	4.96	42.38 12.60	23.82	24.80 15.10	9.70	20.22 12.19	4.43	2.63	0.97
	B	138	43	426 165	218	290 144	146	285 134	104	31	16	1,139	12.12	3.78	37.41 14.49	19.4	25.46 12.64	12.82	25.01 11.76	9.13	2.72	1.40
Alum Precipitated	C	98	16	160 91	53	240 118	122	509 315	145	31	18	1,007	9.73	1.59	15.89 9.04	5.26	23.83 11.72	12.11	50.55 31.28	14.40	3.08	1.79
Combined Vaccine	D	148	86	420 207	127	370 173	197	356 169	125	40	22	1,294	11.44	6.65	32.46 16.0	9.81	28.59 13.37	15.22	27.51 3.06	9.66	3.09	1.70
	E	90	32	220 118	70	220 88	132	326 176	126	24	10	866	10.39	3.70	25.41 13.63	8.08	25.40 10.16	15.24	38.79 20.32	14.55	2.77	1.15

gave 20.22 per cent and 25.01 per cent strong agglutinin titers (1:320 or above), whereas the alum-precipitated vaccine (*C*) gave 50.55 per cent. The pertussis vaccine combined with aluminum hydroxide-adsorbed diphtheria and tetanus toxoids (*D*) gave an intermediate value of 27.51 per cent, whereas, when one dose of fluid vaccine *B* was given between the two doses of vaccine *D* (type E), as recommended by Miller, strong agglutinin titers occurred in 38.79 per cent of the cases.

Sauer[4] has recommended immunization after the age of 7 months on the basis of his finding that only 27 per cent of eighty-nine infants developed strong complement fixing antibodies following immunization with *Hemophilus pertussis* vaccine given at or below the age of 3 months, whereas over 70 per cent of the infants inoculated at an older age showed strongly positive complement fixation tests. In Sauer's study, pertussis occurred seven times more frequently among children inoculated before the age of 3 months than among those inoculated after 7 months of age. A study of his data will indicate, however, that immunization of infants under 3 months of age was of value, since the attack rate in the immunized group was lower than in a similar non-immunized group, the disease in these infants was mild, and none died. Nevertheless, Sauer recommended the seventh month as the optimum age for pertussis immunization.

There have been objections to the agglutination test as a measure of antibacterial immunity. It serves as a convenient method for the determination of only one of many specific antibodies. Our studies show that the quantitative agglutinin titers generally correspond to quantitative complement fixation titers but not to qualitative complement fixation tests which are used by many investigators and which should be abandoned. "These methods of reporting results (1+, 2+, 3+, 4+) and the inference that the number represents a scale of positivity is, however, fundamentally and completely in error and should be abandoned. Classifications based on degree of lysis are devoid of quantitative significance" (Eagle[5]). Furthermore, subsequent studies reveal that the protective power of serum can be correlated quite closely to the agglutinin titers under challenge of exposure.

The data presented seem to indicate that the relatively poor response which Sauer obtained in the young infants may be attributed to the use of fluid vaccine. Perhaps in young infants prolonged antigenic stimulus by alum precipitation is required. In a recent publication,[6] Sauer states: "It has been firmly established that for infants less than six months of age only alum-precipitated pertussis vaccine should be used."

IV. *Evaluation of the Effect of Various Types of Pertussis Vaccine on the Incidence and Severity of Reactions in the Immunization of Young Infants.*—The incidence of local and systemic reactions to the fluid, alum-precipitated, and combined vaccines administered to young infants were analyzed as in our previous communication.[1] The local reactions were measured by the parents and were classified as mild, moderate, and severe, depending on whether their diameters were less than 2.5 cm., between 2.5 and 5 cm., or more than 5 cm. respectively. The fourth category included reactions in which abscess forma-

tion occurred. Small, deep, palpable nodules were not classed as a reaction. The systemic reactions were classed as mild, moderate, or severe depending on whether symptoms persisted less than twenty-four hours and/or were accompanied by a moderate fever or a high fever lasting more than two days, respectively.

A glance at Table V shows that local and systemic reactions occurred far less frequently with the alum precipitated vaccine than with the fluid vaccines and slightly less than with the combined vaccine (anhydrox), but abscesses occurred in 1.5 per cent with the alum vaccine, whereas the fluid and combined vaccine gave abscesses very rarely. Abscess formation with the alum-precipitated vaccine may be avoided by: (1) deep subcutaneous or intramuscular injection as recommended by Bell;[7] (2) avoiding intracutaneous inoculation as recommended by Sako and associates;[1] (3) directing the needle downward as recommended by Sauer.[6] Observations on older children, however, indicate that reactions occur much more frequently with the alum-precipitated vaccine. It was observed in the course of this study that in the immunization of older infants and children the combined vaccine is the product of choice since it gives far less reactions than the fluid product.

V. *Relationship of Local and Systemic Reactions to Agglutinin Titers.*—Local and systemic reactions are productive of agglutinins in higher titer than if no reactions occurred (Table VI). As a general rule, the more severe the reaction the higher the titer. Systemic reactions induced the production of higher agglutinin titers than local reactions. Abscess formation was associated with high agglutinin titers (1:1280 or above) in the fifty-five cases observed.

The mechanism by which reactions produce higher antibody titers is not known. Perhaps greater stimulus is placed on the reticuloendothelial system. Febrile infections often give rise to secondary nonspecific rise in antibodies (anamestic reaction). Numerous studies show that intradermal inoculation is followed by the development of antibodies (Dick test, Schick test, intradermal typhoid immunization). Experiments designed to demonstrate the local formation of antibodies at the site of intradermal inoculation have yielded equivocal results. However, systemic production of antibodies may be efficiently carried out by the skin due to the richness of the dermis in reticuloendothelial cells.

VI. *Duration and Stability of Agglutinin Titers Following Pertussis Immunization of Young Infants With Alum-Precipitated Vaccine.*—Miller and coworkers,[8] Lapin,[9] Mishulow,[10] and others have found that in older infants and children pertussis agglutinins persist in the blood in relatively high titer for several years (two to six years). Miller and associates[8] observed no downward trend in antibody titer. Furthermore, the vast majority evidenced a relatively constant antibody level. A study of Table VII confirms the observation of the authors mentioned above. In young infants, the height of antibody titer is reached in from two to four months after completion of immunization, after which a plateau is maintained for three years or longer. Moreover, analysis of individual cases reveals that the agglutinin titer of any given infant remained fairly constant for the three-year period of observation.

TABLE V. INCIDENCE AND SEVERITY OF LOCAL AND SYSTEMIC REACTIONS IN YOUNG INFANTS FOLLOWING INOCULATIONS WITH FLUID, ALUM-PRECIPITATED, AND COMBINED PERTUSSIS VACCINES

	FLUID VACCINE				ALUM-PRECIPITATED VACCINE		PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (ANHYDROX)			
	TYPE A		TYPE B		TYPE C		TYPE D		TYPE E	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Total inoculations	2,166		3,417		3,021		3,882		2,598	
Local Reactions:										
Mild	247	11.4	301	8.8	157	5.2	228	8.8	285	11.0
Moderate	178	8.2	209	6.1	52	1.7	121	4.7	117	4.5
Severe	78	3.6	76	2.2	5	0.14	39	1.5	71	2.7
Abscess	4	0.2	2	0.06	44	1.5	0		1	.04
Total	507	23.4	588	17.16	258	8.5	388	15.0	474	18.24
Systemic Reactions:										
Mild	269	12.4	324	9.5	184	6.1	249	6.4	249	9.6
Moderate	149	6.9	198	5.8	33	1.1	99	2.6	99	3.8
Severe	50	2.3	62	1.8	7	0.22	47	1.3	49	1.9
Total	468	21.6	584	17.1	224	7.4	397	10.3	397	15.3

TABLE VI. RELATIONSHIP OF LOCAL AND SYSTEMIC REACTIONS TO AGGLUTININ TITERS

REACTIONS	TOTAL	AGGLUTININ TITERS								
		0 TO 1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560
Local Reactions:										
Mild	216	23 (10.8%)	16 (7.7%)	10 (4.9%)	26 (12.2%)	40 (18.6%)	62 (28.7%)	29 (13.7%)	6 (2.8%)	4 (1.7%)
Moderate and severe	137	10 (7.1%)	7 (5.4%)	7 (5.4%)	12 (8.5%)	17 (12.6%)	45 (32.7%	24 (17.2%)	9 (6.7%)	6 (4.4%)
No reaction	265	31 (11.8%)	17 (6.5%)	17 (6.5%)	31 (11.6%)	34 (13.0%)	90 (33.8%)	34 (12.7%)	8 (2.9%)	3 (1.2%)
Systemic Reactions:										
Mild	234	25 (11.0%)	11 (4.7%)	14 (6.2%)	21 (9.2%)	24 (10.4%)	74 (31.7%)	41 (17.7%)	14 (5.9%)	10 (4.3%)
Moderate and severe	168	15 (9.1%)	5 (3.0%)	6 (3.6%)	9 (5.4%)	14 (8.4%)	36 (21.2%)	45 (26.5%)	23 (13.9%)	15 (8.8%)
No reaction	265	31 (11.8%)	17 (6.5%)	17 (6.5%)	31 (11.6%)	34 (13.0%)	90 (33.8%)	34 (12.7%)	8 (2.9%)	3 (1.2%)

TABLE VII. DURATION AND STABILITY OF AGGLUTININ TITERS FOLLOWING PERTUSSIS IMMUNIZATION WITH ALUM-PRECIPITATED VACCINE IN 786 YOUNG INFANTS

TITER	AFTER COMPLETION OF IMMUNIZATION					
	2 TO 6 MO.	6 TO 12 MO.	12 TO 18 MO.	18 TO 24 MO.	24 TO 30 MO.	30 TO 36 MO.
1:2,560	13	15	17	12	16	15
1:1,280	24	23	25	33	29	28
1:640	123	122	131	150	171	148
1:320	259	265	261	236	215	235
1:160	99	92	97	91	95	86
1:80	99	104	98	104	104	108
1:40	37	42	40	32	31	38
1:20	51	47	44	48	60	59
1:10	30	23	25	35	21	29
0	51	53	48	45	44	40

VII. *Effect of "Stimulating Dose" of Pertussis Vaccine on the Agglutinin Titers of Infants Immunized Below the Age of 3 Months.*—Young infants below the age of 3 months were immunized with the alum-precipitated pertussis vaccine (40 billion per cubic centimeter) as previously described. The agglutinin titers were determined two to four months following completion of immunization and again just before 0.5 c.c. of the "stimulating dose" which was approximately eight to twelve months after the last inoculation. It can be readily seen (Table VIII) that within one month after revaccination the agglutinin titers rose markedly in the vast majority of cases. It is interesting that some children with negative titers were never able to develop any antibodies in spite of repeated "stimulating" inoculations. All cases exposed to pertussis were excluded from this study.

TABLE VIII. EFFECT OF "STIMULATING DOSE" OF 0.5 C.C. ALUM-PRECIPITATED PERTUSSIS VACCINE ON THE AGGLUTININ TITERS OF 368 INFANTS IMMUNIZED BELOW THE AGE OF 6 MONTHS

TITER	BEFORE "STIMULATING DOSE"	AFTER "STIMULATING DOSE"				
		1 MO.	6 MO.	12 MO.	18 MO.	24 MO.
1:2,560	6	56	58	56	58	65
1:1,280	11	183	123	139	130	132
1:640	65	85	59	55	56	66
1:320	114	54	45	44	51	42
1:160	47	27	24	23	22	15
1:80	45	15	16	15	11	12
1:40	20	8	7	9	12	10
1:20	24	14	12	14	14	16
1:10	15	9	8	6	7	5
0	21	7	6	7	7	6

VIII. *Incidence and Severity of Pertussis Upon Exposure in Immunized and Nonimmunized Children with Known Agglutinin Titers.*—Out of over 40,000 young infants below 3 months of age who were immunized with pertussis vaccines, 493 whose agglutinin titers were known and followed periodically every three to six months were exposed to pertussis within the household. As controls, 438 young nonimmunized infants of comparable age, whose agglutinin titers were negative and who were similarly followed periodically, were exposed to pertussis. The diagnosis of pertussis was made clinically by the author after

thorough examination and repeated observations. Table IX shows conclusively that the incidence and severity of pertussis was far greater among the nonimmunized (89.7 per cent) than in the immunized (13.2 per cent). It is very significant that pertussis did not occur in the immunized children with agglutinin titers of 1:320 or above in spite of prolonged exposure, the exposed child often sleeping in the same bed with an older child having the disease. On the other hand, many exposed children with low or negative agglutinin titers also escaped the disease. This supports Miller's observation[11] that, although immunity may exist in the absence of agglutinins, susceptibility is not present in the presence of agglutinins in high titer (1:320 or above).

TABLE IX. INCIDENCE AND SEVERITY OF PERTUSSIS UPON INTIMATE FAMILIAL EXPOSURES IN IMMUNIZED AND NONIMMUNIZED CHILDREN WITH KNOWN AGGLUTININ TITERS

TITER	TOTAL	CASES	PER CENT	SEVERITY			ESCAPES	
				MILD	MOD.	SEVERE	NO.	%
				*Immunized**				
1:2,560	12	0	0.0				0	100.0
1:1,280	27	0	0.0				0	100.0
1:640	48	0	0.0				0	100.0
1:320	62	0	0.0				0	100.0
1:160	53	6	11.3	6	0	0	47	88.7
1:80	75	8	10.7	7	2	0	67	89.3
1:40	91	17	18.7	12	4	0	74	81.3
1:20	82	21	25.6	18	2	1	61	75.4
1:10	16	4	25.0	2	1	1	12	75.0
0	27	9	33.3	4	3	2	18	66.7
Total	493	65	13.2	49	12	4	279	86.8
				Nonimmunized controls†				
Titer negative	438	393	89.7	43	291	59	45	10.2

*No deaths.
†Three deaths.

SUMMARY

Contrary to popular opinion, young infants are able to produce antibodies as a result of pertussis immunization just as well as older children. In the immunization of these young infants, prolonged antigenic stimulus as afforded by alum precipitation is necessary for efficient antibody production. The alum-precipitated vaccine, except for its tendency to produce sterile abscesses, gave far less local and systemic reactions than the fluid or combined vaccines. Severe reactions were an infrequent occurrence with the young infants. Local and systemic reactions were associated with high agglutinin titers indicating that, although undesirable from the practical standpoint, they are highly desirable immunologically.

Following pertussis immunization the agglutinins reach a plateau level in two to four months and remain at this level practically unchanged for at least three years. A "stimulating dose" of pertussis vaccine administered eight to twelve months following completion of immunization of young infants raises the agglutinin titer to higher levels within one month, after which the plateau is maintained for two years or longer.

A follow-up of immunized and nonimmunized children with known agglutinin titers shows that immunization of young infants below 3 months of age is highly effective and supports the contention that, although immunity may exist in the absence of agglutinins, susceptibility does not occur in the presence of agglutinins in high titers (1:320 or above).

RECOMMENDATION

Data have been presented to show that immunization of young infants below 3 months of age is immunologically sound and highly effective if an alum-precipitated vaccine is used. On the basis of these findings, physicians are urged to institute a program of early immunization against pertussis on a nationwide basis.

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THE TREATMENT OF ALLERGIC PATIENTS WITH BENADRYL

A Report of Seventy-nine Cases

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THE problem of effecting a practical and suitable therapeutic antihistamine agent with comparatively safe and little toxic properties occupied the minds of investigators for many years. Atropine was used, but the dosage had to be too great to be of any clinical use. Dale and Richards,[1] in 1918, used epinephrine, which proved too potent and fleeting to be practical. Bovet and Staub[2] of France, in 1937, made a systematic search among the Fourneau series of chemicals for a practical antihistamine compound and developed two potent antihistamine substances known as 1571 F and 929 F. However, the disagreeable and toxemic responses to these drugs made their clinical usefulness impossible. Mayer and associates,[3] in 1945, synthesized a similar but less toxic antihistaminic chemical compound known as a-pyridinoethylenediamine. About the same time, in the research laboratories of Parke, Davis & Co., Rieveschl and Huber synthesized the antihistaminic chemical compound known as Benadryl (B-dimethylaminoethyl benzyhydryl ether hydrochloride). Loew and his associates,[4] working in the same laboratories, tested the toxicity of benadryl in rats and guinea pigs, and found it to be very low. They also made pharmacologic studies of its effects upon animals. In an untreated control group of guinea pigs with induced histamine shock they obtained 100 per cent mortality rate. When adequate doses of aminophyllin were offered to a group of animals with histamine shock, the mortality was 47 per cent, and when such guinea pigs received benadryl the mortality rate was zero. Loew noted immediate relief of the bronchial spasm and vasomotor depression in the benadryl treated animals. Hallenbeck and associates[5] studied the antispasmodic effect of benadryl upon histamine treated, ileum muscle strips, in vitro, and found it 650 times as effective as papaverine in antispasmodic effect. Curtis and Owens,[6] in 1945, administered benadryl to eighteen allergic patients, reporting therapeutic effectiveness and low toxicity. McElin and Horton[7] observed a patient known to have hypersensitiveness to cold. The blood histamine of this patient had risen during and immediately after a period of active response to cold, demonstrating that "H" substance in this case was definitely histamine. They produced a typical wheal and flare on the patient's forearm by holding a standard sized ice cube on one spot for three minutes. Then benadryl was given intravenously for ten minutes and the cube of ice was applied to the opposite forearm for a similar period. Response to the ice cube on this occasion was estimated to be about 50 per cent less than that produced before the giving of benadryl. This may be one of the most definitive demonstrations of histamine antagonism. The symposium on benadryl as an antihistamine substance and its use in urticaria, bronchial asthma, and hay fever, and allergic diseases of childhood[8] confirm the findings of Curtis and Owens[9] and of Loew and associates.[9]

PLAN OF STUDY

In a recent clinical study from January, 1946, to July, 1946, the value of benadryl was tested by administering it to seventy-nine patients with allergy. The results are tabulated in Table I. In Tables II and III the dosage and duration of treatment and the secondary effects of benadryl are recorded.

TABLE I. RESULTS IN SEVENTY-NINE PATIENTS WITH ALLERGIC CONDITIONS

DIAGNOSIS	CASES (NO.)	AGE (YR.)	SEX		RESULTS			
			M	F	EXCELLENT	GOOD	FAIR	NOT IMPROVED
Recurrent, chronic urticaria	8	3-6	5	3	8	0	0	0
Urticaria with angioneurotic edema	3	2-5	1	2	3	0	0	0
Hay fever, spring and early summer, seasonal	23	4-11	10	13	19	3	1	0
Hay fever and asthma	6	9-12	3	3	4	1	1	0
Asthma	9	10-35	6	3	6	0	1	2
Vasomotor rhinitis	13	6-16	7	6	13	0	0	0
Polypoid ethmoiditis with alternate nasal clogging and drip with forced mouth breathing, rhinorrhae, and dyspnae	2	16 and 30	2	0	1	1	0	0
Acute urticaria, food allergy of fish, berry, and spinach	4	6-10	2	2	4	0	0	0
Migraine type cephalgia	3	13-20	1	2	0	1	1	1
Ménière's disease	4	16-30	0	4	0	1	1	2
Contact dermatitis with eczematous lesions	4	6-16	3	1	1	2	0	1

TABLE II. DOSAGE AND DURATION OF BENADRYL TREATMENT IN SEVENTY-NINE CASES

AGE (YR.)	CASES (NO.)	DAILY DOSE (MG.)		DURATION OF TREATMENT	REMARKS
		MINIMUM	MAXIMUM		
2	2	20	50	One month	For attacks and continuance; administered elixir benadryl, each teaspoon equals 10 mg.
3 to 6	34	30	50	One week to two months	Benadryl Kapseals, each 50 mg.; elixir given to young child
6 to 13	30	100	150	Two weeks to two months	Three children received the maximum dose for two days, then the minimum dose; others, minimum
13 to 16	5	100	150	One month to three months	One child received maximum dose for three days and felt too sleepy; dose reduced to minimum
Above 16	8	100	200	Two weeks to five months	Two cases tolerated maximum dose; three received 150 mg.

TABLE III. SECONDARY EFFECTS; ANALYSIS OF SEVENTY-NINE CASES

SECONDARY EFFECTS	CASES	REMARKS
Drowsiness	45	Very mild in most patients
with vertigo	6	The symptoms were mild to moderate.
with diplopia	2	25 mg. pyridoxine given with benadryl
with dry mouth	26	diminished or cleared up the secondary
with fatigue	3	effects and drowsiness; in two cases,
without other symptoms	8	50 mg. niacinamide daily was necessary
Jittery feeling	16	Reduced the maximum dose to the daily minimum dosage; symptoms cleared up
Mild nausea and bad taste in mouth	3	Pyridoxine, 25 mg. daily, gave relief
No side effects	15	

Benadryl was given during attacks of urticaria whether it was an acute condition, a recurrent or chronic attack. The response was noticeable in one-half to one hour after administration and lasted about twelve hours. Similar favorable responses were observed in children with hay fever, those who suffered from asthma, and the sufferers from hay fever and asthma combined. In three adult asthma patients, one showed a fair response and two showed no improvement. The vasomotor rhinitis and polypoid ethmoiditis individuals responded miraculously to the benadryl therapy. The contact dermatitis patients with or without eczema gave moderately fair results, while the migraine type of cephalgia and the patients with Ménière's disease responded from fair to poor. All were treated for the attacks and given the maximum daily dose of benadryl as shown in Table II. If relief was obtained, continuous treatment with minimum dosage of benadryl was given daily for periods varying from one week to two months, depending upon the condition and the individual patient. This regimen of treatment, continuing the administration of benadryl, allows the child to eat the allergic foods or live in a pollen saturated area, and at the same time be kept free from symptoms. One child suffered from severe hives when eating spinach. While taking benadryl, she was able to eat a saucerful of spinach and yet be free from any wheals or flare-ups. Several children were attacked with severe asthma wheezing and dyspnea in the presence of fish in the home. While taking benadryl, the same children were able to eat fish and be entirely free from asthma attacks. The treatment with benadryl was kept up from four to eight weeks, after which most children remained free from recurrent attacks of their allergic disease. In a few instances where children had a relapse of allergic symptoms of their condition they received another course of treatment with benadryl for one or two months. In every case benadryl was administered beginning with the minimum dose for the age of the patient, and if there was no therapeutic response in from one-half to one hour the dose would be considered inadequate and hence increased.

DISCUSSION

Benadryl appears to belong to a pharmacologic group which has the property of preventing some of the pharmacologic effects of histamine. Histamine seems to be held as such within the cells and released rapidly when they are damaged. The release of histamine or histamine-like substances has been held responsible in whole, or in part, for the presenting complaint in the majority of cases reported in Table I. Benadryl seems to diminish the amount of histamine to be released in the cells, thereby relieving the symptoms of the allergic patients. Benadryl may also act at the source of change of histadine to histamine through the carboxylase bacteria. Our present knowledge of the pharmacologic action of benadryl and our observations of its therapeutic action clinically in allergic patients, leads us to conclude that it offers symptomatic relief in urticaria, vasomotor rhinitis and ethmoiditis, in hay fever and asthma of children, and other allergic manifestations.

SUMMARY

The clinical findings in seventy-nine allergic patients treated with benadryl, of whom seventy-one are children and eight adults, are reported. The ages of the children are from 2 to 16 years, and the adults from 19 to 35 years, with their sex about equally distributed. The favorable responses to benadryl administration show 76 per cent of all groups have excellent improvement, 10 per cent good, 6 per cent fair to poor, and 8 per cent no improvement. It is interesting to note that when pyridoxine hydrochloride 25 mg., was added to each dose of benadryl, the drowsy feeling wore off. This was found particularly useful for students especially when they had to attend lecture courses. It also diminshed nausea, vertigo and diplopia, these occurring but rarely. In two patients on whom pyridoxine hydrochloride did not remove the secondary effects, 50 mg. niacinamide were given, and the side effects of vertigo and nausea were immediately relieved. In general, the side effects or toxicity from benadryl were very mild, while its therapeutic effects were potent and beneficial. Benadryl can be administered safely and effectively. It should be used with caution and only where indicated.

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TREATMENT OF ACUTE DIARRHEA IN THE CINCINNATI GENERAL HOSPITAL DURING THE YEARS 1944 AND 1945

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DIARRHEA and enteritis, considered as an entity, ranks second in the causes of death in infancy and childhood.[1] It occupies, by virtue of its high morbidity, a large part of many pediatric services in this and other countries. Annually, in the five years from 1935 to 1940 over 10,000 children in the United States under 2 years of age died of diarrhea. In Cincinnati between 1939 and 1941 there were three times as many deaths from diarrhea as from diphtheria, scarlet fever, and pertussis combined.[2] Despite local efforts to prevent and treat the disease, Cincinnati's resident death rate from diarrhea compared with cities of comparable size is among the highest in the country. The white death rate is 50 per cent above the average, the Negro rate 12.5 per cent below the average of thirteen cities (1939 through 1941).

Compared with similar data compiled from 1929 through 1931, there has been some improvement. During the earlier period Cincinnati had the highest white death rate, while it now has the fourth highest. The Negro death rate in 1929 through 1931 was also highest; now it is sixth highest.

In Cincinnati we therefore have had an opportunity to study large numbers of cases of severe, neglected diarrhea each year, and have tried many types and plans of therapy. In the past two years at the Cincinnati General Hospital we have employed continuous intravenous therapy with great success in the treatment of all children acutely ill with diarrhea. The methods and techniques employed have evolved gradually over the two-year period as a result of clinical experience both at Cincinnati Children's Hospital and Cincinnati General Hospital. No single new procedure of therapy has been devised; what is new to a certain extent is the emphasis on consistent, planned, continuous, intravenous therapy, the duration and character of which is determined by the clinical course of the disease and the derangement of the fluid balance of the patient.

I. *Plan of Therapy.*—On admission, the patient is taken at once to the treatment room. Blood is drawn for determination of the carbon-dioxide combining power and serum chloride. A stool culture is obtained at this time. A needle is inserted into the patient's wrist or foot for continuous intravenous fluid administration. The fluid therapy is begun with normal saline. About 10 c.c. per pound of body weight is given by injection over a period of several minutes, and then the continuous intravenous drip is started either with saline or 5 per cent glucose in saline, the drip being regulated to provide at an even rate the estimated fluid required over the next twenty-four hours. The fluid requirement in the first twenty-four hours following admission is calculated from

From the Children's Hospital Research Foundation and the Pediatric Department of the University of Cincinnati School of Medicine.

simple empirical rules. If the patient is moderately dehydrated, he receives his usual saline requirements of 100 to 125 c.c. for infants,[3] plus an additional 5 per cent of his body weight as saline-containing fluid; physiological saline, glucose in saline, plasma, blood, or any combination of these fluids. If severely dehydrated, he receives the daily saline requirements plus 10 per cent of his body weight as saline-containing fluids. Within an hour after admission, the blood carbon-dioxide combining power has been reported. If it is less than 30 volumes per cent, it is corrected to 40 to 45 volumes per cent by the injection of 3.75 per cent sodium bicarbonate solution, following which the continuous drip is resumed; if the carbon-dioxide combining power is greater than 30 volumes per cent, no correction is usually made.

TABLE I. DIARRHEA AND ENTERITIS IN THIRTEEN CITIES OF THE UNITED STATES

RESIDENT DEATH RATES (PER 100,000 POPULATION) OF INFANTS UNDER 2 YEARS OF AGE*			
WHITE RACE		NEGRO RACE	
CITY	DEATH RATE	CITY	DEATH RATE
Cleveland	64	Kansas City	36
St. Louis	75	Cleveland	114
Memphis	79	Memphis	165
Kansas City	86	Birmingham	243
Birmingham	109	Pittsburgh	265
Atlanta	156	Indianapolis	290
New Orleans	159	St. Louis	304
Indianapolis	172	*Cincinnati*	*378*
Pittsburgh	189	New Orleans	406
Cincinnati	*247*	Columbus	482
Baltimore	250	Atlanta	499
Columbus	272	Washington	748
Washington	300	Baltimore	840
Average of thirteen cities	164	Average of thirteen cities	433

*Average of 3 years (1939 through 1941).

Thereafter, in each twenty-four-hour period the patient is given enough saline-containing fluid to satisfy his daily requirement (100-125 c.c.) and, if diarrhea continues, to replace electrolyte lost in the stools. The remainder of the daily fluid intake (based on a minimum daily requirement of 120 c.c. per kilogram or 2¼ ounces per pound) is given as 5 per cent glucose in water. Plasma is given on admission instead of normal saline solution if the patient is in shock or severely malnourished. Whole blood transfusions are frequently employed after hydration is accomplished, as the hemoglobin concentration often falls to values of 7 to 9 Gm. per cent following restoration of circulating blood volume.

Each patient's "intravenous progress" is followed on two sheets: one sheet is kept by the nurses to indicate the type and amount of fluid administered, and one is kept by the house staff to summarize the intake of calories, protein, saline-containing fluids, and total fluid volume for each twenty-four-hour period.

Often the diarrhea subsides completely within twenty-four to thirty-six hours, and at this point small amounts of 5 per cent glucose in water or saline (½ to 1 ounce) are given by mouth every three hours. If the initial two feedings of clear fluid are retained, formula, either boiled, skimmed milk or skimmed

milk plus 10 per cent corn syrup, is fed in small amounts (about 1 ounce) every three hours. The intravenous infusion by that time is usually discontinued. Skimmed milk is then given every three hours for twenty-four hours, and, if there is no recurrence of the diarrhea, is increased gradually in amount until the patient is receiving his daily fluid requirement by mouth. Until this time hypodermoclyses are given once or twice a day to supply as much extra fluid as is necessary to make up the total fluid requirement. Usually, after two to four days, the patient can be changed to an evaporated milk formula, and discharged within one to three days thereafter.

Sulfadiazine or sulfathiazole is given routinely to all patients shortly after admission, and continued until at least one negative stool culture is received from the laboratory. The drug is given subcutaneously every twelve hours while oral feedings are withheld, and thereafter is given orally every four hours in doses of grains 1 to 1½ per pound of body weight. Clinically, the course of the disease has not seemed to be affected by the administration of sulfonamides. There were only twenty-six patients in the two years (1944 through 1945) with proved dysentery, and it is in these patients alone that sulfonamide therapy is of benefit. A previous series of cases of diarrhea reported in 1941 by Cooper and others[4] failed to disclose a statistically demonstrable effect of sulfathiazole in the treatment of patients whose stools were negative for the dysentery organism.

For cases of chronic diarrhea the therapy is modified so that in addition to satisfying the daily needs for fluid and saline, as in the acute cases, the caloric and protein requirements are also met. To do this, a venesection is usually necessary, because of the hypertonic solutions used. Ten per cent glucose in water, 5 per cent casein hydrolysate solution in 10 per cent glucose, 5 per cent glucose in normal saline, plasma with 50 per cent glucose added (to make the equivalent of 10 per cent glucose in plasma) are used to provide at least 40 calories per pound and 1 to 2 Gm. of protein or amino acids per pound.

Following is the case report of a patient admitted during the summer of 1945 which may serve to illustrate the type of therapy employed.

CASE REPORT

W. M., a 6-week-old, white, male infant was admitted Aug. 20, 1945, with a history of diarrhea for two days, and vomiting for one day. He had been on a formula of evaporated milk since birth, and had had a previous bout of gastroenteritis. Physical examination on admission showed the infant to be very thin and malnourished, weighing 7 pounds, 1 ounce. Dehydration was marked, and the patient appeared acidotic.

Laboratory Studies.—Carbon-dioxide combining power, 24 volumes per cent; hemoglobin, 12.5 Gm. per cent; white blood cell count, 11,300; stool culture negative; urine negative.

Course.—A continuous intravenous infusion was started at 12 noon on Aug. 20, 1945, with 40 c.c. of 3.75 per cent sodium bicarbonate solution, followed by 275 c.c. of normal saline, and then 100 c.c. of 5 per cent glucose in saline and 120 c.c. of plasma, in addition to 500 c.c. of 5 per cent glucose in water. The diarrheal stools continued. On Aug. 22, 1945, the diarrhea ceased completely; the intravenous infusion was discontinued, for technical reasons, and the patient given an additional subcutaneous infusion later in the day. On Aug. 23, 1945, hypodermoclyses were again given, and the patient was started on 1 ounce of glucose water orally every two hours. After the patient had retained four of these feedings, skimmed milk was

started, in 1 ounce amounts. On Aug. 24, 1945, the skimmed milk was increased to 2 ounces every three hours; one hypodermoclysis of 5 per cent glucose in saline was given (200 c.c.); on that day the patient had three semisolid stools. On Aug. 25, 1945, the stools were normal and the skimmed milk was increased to 3 ounces every three hours; and on Aug. 26, 1945, the patient was placed on a standard evaporated milk formula, 4 ounces every four hours.

Sulfadiazine every twelve hours was given subcutaneously until Aug. 23, 1945 (grains 3½); thereafter, it was given orally, grains 1½ every four hours.

Clinically, the patient responded rapidly to the intravenous fluids, with prompt disappearance of the lethargy and irritability noted on admission; he took his feedings eagerly, as do most of the patients after a period of oral starvation. He was discharged on his eighth hospital day weighing 8 pounds 14 ounces.

II. *Complications of Therapy.*—Superficial areas of necrosis were noted several times in debilitated patients, at points where the arm or leg splints were inadequately padded; these healed with little or no scarring. One patient developed wrist drop from extreme flexion of the wrist; this cleared over a period of several months. There were three recorded cases of localized abscesses, all of which healed following incision and drainage. Thrombophlebitis and cellulitis about the site of the needle was often seen, but healed after treatment with massive wet saline compresses and sulfonamides. The only serious and permanent indictment of the therapy was the case of an infant who developed a cutaneous slough of the right wrist and gangrene of the left leg following continuous intravenous infusions containing calcium chloride; a supracondylar amputation was required for the left leg; the arm healed, but scarred with a moderate extension contracture.

III. *Results.*—In this series are included all of the patients with acute diarrhea or dysentery admitted to the pediatric ward of the Cincinnati General Hospital during 1944 and 1945, a total of 292 cases. Only patients with a discharge diagnosis of diarrhea, enteritis or bacillary dysentery are included; no patients with an additional diagnosis of any acute or chronic parenteral infection were studied. No cases were excluded except those which developed in premature infants, who are cared for in a separate nursery. The therapy was in all instances carried out by interns under the direction of a pediatric resident. The patients were all seen initially in the admitting room by the pediatric resident, at whose discretion they were admitted to the ward. Of all the patients with diarrhea in the outpatient department, only the most seriously ill were admitted, both because of shortage of beds and nursing help, and a reluctance to overburden the interns with mild cases that could be treated on an outpatient basis. Criteria for admission usually were: (1) marked dehydration and fever; (2) clinical acidosis; (3) persistent vomiting; and (4) failure of simple outpatient treatment measures. In 1944, 34 of 160 patients with diarrhea at the Cincinnati General Hospital received no parenteral fluids; in 1945 only 4 of 132 failed to receive parenteral fluids, an indication not of the increasing incidence of dehydrated patients so much as of an increased awareness on the part of the resident staff that even mildly dehydrated patients should have their fluid and electrolyte volume restored and that infants on insufficient oral feed-

ings to supply minimum needs of fluid require parenteral supplementation until adequate oral feedings are resumed. We think that it may be said that we deal with as severe cases of diarrhea as can be found reported anywhere in the literature.

Of the 292 patients with diarrhea included in this study, 223 were white, 69, Negro. There was a total of 22 deaths, 21 of these occurred in the white infants, one in a Negro infant. In 1944, 12 of 160 patients died, a fatality rate of 7.5 per cent; in 1945, 10 of 132 patients died, a fatality rate of 7.6 per cent. The combined fatality rate for the two-year period was 7.5 per cent, a 9.4 per cent fatality rate for the white race, and 1.5 per cent for the Negro.

Breaking this down into age groups gives a clear idea of the distribution of the disease in our series.

TABLE II. AGE DISTRIBUTION OF MORTALITY FROM DIARRHEA

AGE (MONTHS)	CASES	DEATHS*	FATALITY RATE (%)
0-3	87	11	12.6
4-6	66	6	9.1
7-12	68	3	4.4
13-18	27	1	3.7
19-36	20	0	0.0
37 up	24	1	4.2

*It may be seen from this table that in 221 infants under one year of age twenty deaths occurred, a fatality rate of 9.1 per cent.

In an attempt to classify the severity of the disease in each patient, each case was placed in one of four categories: (1) *Mild*—diarrhea ceasing soon after admission and requiring little or no therapy; (2) *Moderate*—the variety of summer diarrhea that makes up the bulk of the admissions, with carbon-dioxide combining powers of 30 to 40 volumes per cent, fever, and moderate dehydration; (3) *Severe*—carbon-dioxide combining powers of 25 to 30 volumes per cent, fever, and marked dehydration; (4) *Very severe*—carbon-dioxide combining power less than 25 volumes per cent; extreme dehydration; high fever; patients often in shock or in extremis on admission.

TABLE III. SEVERITY AND MORTALITY OF DIARRHEA CLASSIFIED ACCORDING TO AGE

AGE (MONTHS)	NUMBER OF CASES			
	MILD	MODERATE	SEVERE	VERY SEVERE
0-3	3	37	26(1)*	21(10)
4-6	2	37	17	10(6)
7-12	5	42	16	5(3)
13-18	2	17	7	7(1)
19-36	3	12	4	1
37 up	4	17	2	1(1)
Total	19	162	72(1)	45(21)

*Figures in parentheses indicate deaths.

In many instances, critically ill patients had high carbon-dioxide combining powers on admission, and we feel that the carbon-dioxide combining power cannot be considered a reliable guide to the severity of illness, but only to the severity of the concomitant acidosis. Nevertheless, we have kept the carbon-

dioxide combining power as a criterion of the seriousness of the disease, as it is one of the few objective measurements available. Carbon-dioxide combining powers under 40 volumes per cent were reported on the charts of 145 patients; 21 additional carbon-dioxide combining powers were reported from 41 to 50 volumes per cent; 126 patients had no blood carbon-dioxide combining power reported, the great bulk of these being in the first half of 1944, during which time our present plan of therapy was being crystallized.

It is difficult to resist the temptation to exclude certain cases and arrive at a "corrected mortality rate." There were twenty-two deaths in our series; of these, three occurred in patients who died within three hours of admission, before adequate therapy had been instituted. Another three were patients who died of other causes after their diarrhea had subsided: one had multiple congenital heart defects at autopsy and was marantic on admission, weighing 6 pounds at the age of 4 months, another died of a spontaneous pneumothorax on the eighth hospital day, and the third died on the sixteenth hospital day, following an episode of vomiting several days after all diarrhea had ceased. If one excludes these cases in which either the diarrhea was not the obvious cause of death or in which therapy could not be instituted before death, one arrives at a "corrected case fatality rate" of 5.6 per cent (sixteen deaths in 286 cases).

ETIOLOGY

1. *Feedings.*—The clinical impression that breast-fed babies do not contract diarrhea, or, if they do, contract a mild form of the disease that does not necessitate hospitalization or interruption of breast feedings, is amply supported by the fact that of the 221 infants in this series, only three were being breast-fed at the time of admission; one of these patients had such a mild diarrhea that he probably should not have been admitted, one had a chronic low-grade diarrhea, and only one had an acute diarrhea that had to be treated with continuous intravenous therapy.

2. *Specific Etiology.*—In 1944, in 140 of the 160 cases, one or more stool cultures were reported; 26, or 18.5 per cent, of these were positive for dysentery bacilli. In 1945, in 100 of 132 cases, stool cultures were reported; 8, or 12 per cent, of these contained dysentery bacilli. Two cultures revealed *Salmonella paratyphi B.* A number of the stool cultures were positive for *Shigella dispar,* the pathogenicity of which is open to question.[5] Disregarding the disputable virulence of these latter organisms, there were positive cultures for dysentery in 34 of 240 cases. Extrapolating, one can predict that 41 positive cultures would have been obtained had there been stool cultures in all 292 cases. There was one death from bacillary dysentery. Both patients with paratyphoid infection recovered; of the 249 patients with nonspecific diarrhea, 21 died. In other words, excluding all actual and predicted cases of specific diarrhea, the over-all death rate for all cases of acute nonspecific diarrhea is 8.5 per cent. This is one per cent higher than the death rate for the entire series, and may indicate that with the advent of sulfonamide therapy dysentery has become a less fatal disease in infancy than nonspecific diarrhea. Although at one time

parenteral infection was thought to be a common cause of severe diarrhea and vomiting in infancy, and is still so considered both in Great Britain and France, the diarrhea which occurred in infants at the Cincinnati General Hospital suffering primarily from parenteral infection was almost always so mild in nature as to affect little the prognosis of the basic disease and to require little additional therapy. As was stated earlier, all cases in which diarrhea was apparently secondary to parenteral infection were excluded from our series.

3. *Epidemiology.*—One is continually impressed by the part that poverty, ignorance, and substandard living conditions play in the production of diarrhea in infancy. Inability to comprehend feeding instructions, lack of money to comply with them even when the understanding is present, and inadequate housing, sanitary, and cooling facilities, are all factors that impress one after even a brief experience with the parents of these children. With the high incidence of diarrhea in Cincinnati and the infrequence of diarrheas in the more northern metropolitan areas one might think that climate would be a decisive factor; yet Memphis, Birmingham, Atlanta, and New Orleans all had lower white mortality rates than Cincinnati, and, of these more southerly cities, all but Atlanta had lower Negro rates,[2] suggesting that latitude is only a minor factor in the epidemiology of this disease. The majority of cases of diarrhea in Cincinnati come from an area which is inhabited by the poorest of the population, yet in the midst of the greatest concentration of diarrhea in this area there is an oasis, the government housing projects with adequate sanitation, refrigeration, and screening, from which only five of the 292 cases were admitted, while numerous cases dot the map in areas immediately adjacent to and surrounding these homes.

COMPARISON WITH OTHER SERIES

It is instructive to compare our series of cases with those reported elsewhere, difficult as it is to evaluate the severity of cases of diarrhea from different communities and in different years. In 1922 Monrad[5] reported from Stockholm the results of therapy with a "protracted water-diet": patients were starved from three to twelve days, and given water only by mouth and subcutaneous saline as needed. There were 50 deaths in 291 patients; of these, 131 had mild diarrhea, of whom 6 died and 21 developed chronic diarrhea; 160 of the patients were apparently sick enough to be compared with ours, and of these 44 died, and 29 developed chronic diarrheas, a mortality rate of 27.5 per cent. Four years later (1926) Powers[6] reported from New Haven in one of the first papers on planned therapy in infants with severe diarrhea, or, as he called it, "intestinal intoxication." He used subcutaneous and intraperitoneal fluids to combat dehydration, and gave liberal transfusions of whole blood. Food was withheld until toxic symptoms had greatly diminished; thereafter it was given in small, slowly increasing amounts. In 36 patients treated with planned therapy, only 12 died (33 per cent); of 19 not given this treatment, 14 (70 per cent) died. He omits from his series 9 patients who died within twelve hours of admission or were taken home against advice. In 1931 Karelitz and Schick[7] published the first paper on continuous intravenous treatment of diarrhea, an outgrowth

of observations that patients with surgical shock respond well to intravenous glucose solutions and that severe diarrhea is in many respects similar to surgical shock. When the patients with diarrhea were given intravenous infusions they responded well but often relapsed when the infusion was discontinued, hence, the idea of continuous intravenous therapy until the danger of relapse had passed. In the first year he reported 30 cases of very severe diarrhea, with only 7 deaths, and the following year 53 cases, with only 6 deaths, a marked improvement on the mortality rates that prevailed at that time. In 1934 Lyon and others[8] reported 821 cases of diarrhea treated at Cincinnati General Hospital from 1923 to 1932, with a mortality rate of 32.4 per cent. They also described the use of continuous intravenous therapy, as outlined by Karelitz, on 17 severely ill patients, of whom 8 died; some of these patients were also suffering from pneumonia. Cohen and others[9] recorded their experience in 1933 with continuous intravenous treatment, and also extensive chemical determinations on blood, urine, and stools during the period of the diarrhea. Their series included 9 patients, of whom 2 died (2 had concomitant otitis media, and 2 had pneumonia).

More recently, several series of cases have been reported from England. Much of the diarrhea was thought to be secondary to parenteral infection and in most series the death rate was exceedingly high. Smellie[10] reported 500 cases in Birmingham, England, with 240 (48 per cent) deaths. Of these, 321 had some type of parenteral infection. Campbell and Cunningham[11] reported 574 cases of diarrhea from London during the period January, 1937 through August 1939. They divided their cases into "dehydrated" and "non-dehydrated"; in the first group there were 152 deaths in 283 cases (53.7 per cent); in the second, 7 deaths in 291 cases (2.4 per cent). They noted a 30.5 per cent incidence of parenteral infection. Their therapy consisted of starvation for twenty-four to forty-eight hours, giving clear fluids orally or continuous subcutaneous Ringer's glucose-saline. From Britain again there is a report by Field and others[12] in 1943, citing 100 cases with 23 deaths (23 per cent). For marked dehydration they employed continuous intravenous Hartmann's solution for twenty-four hours, and then instituted a "pyloric feeding schedule." It is interesting to note that the British authors who employ continuous intravenous therapy use mainly Hartmann's solution, Ringer's solution, or normal saline.

The outstanding British paper as far as successful therapy is concerned is a report in 1944 by Alexander and Eiser from London.[13] They describe 150 cases of children under 15 months of age, with only 8 deaths. The series includes 88.6 per cent of patients with evidence of parenteral infection, chiefly otitis media and mastoiditis. Their therapy consisted of sulfathiazole and clear fluids for twelve to twenty-four hours, followed by dilute feedings in the milder cases; the severer, dehydrated cases were given intravenous fluids, alternating with half-strength plasma (diluted with Hartmann's solution) and Hartmann's solution, until the patients were able to take oral fluids. Of these cases, only 69 were dehydrated; all the deaths were in this group. If we take of these cases only the dehydrated ones as comparable to those in our series the mortality

rate becomes practically 12 per cent. Finally, there are 215 cases from Middlesex, England, reported by Gairdner[14] in 1944, with 109 deaths (51 per cent). Thirty-five per cent of these patients had parenteral infections. The death rate was the same in those without or those with parenteral infection. Continuous intravenous therapy was employed in the more acutely ill patients, but the author's comment is that "it could be relied on to correct dehydration, but only too often failed to save life."

Two recent reports from the United States present encouraging statistics on the results of present-day therapy of infantile diarrhea. From Louisville in 1944 Glaser and Bruce[15] reported 180 cases seen from 1940 to 1942, with 32 deaths (17.8 per cent); in 1942 there were 6 deaths in 58 cases, a death rate of only a little over 10 per cent. Their therapy includes continuous intravenous fluids for thirty-six hours in the more severely ill patients, followed by oral feedings of low caloric formula every three to four hours, allowing the infant to regulate his intake at will. This regime, without the intravenous fluids, is used on the milder cases also, after an initial twelve hours of starvation. All patients received sulfonamide. Govan and Darrow[16] during the summer of 1945 were able to achieve the remarkably low "corrected mortality rate" of 6 per cent in 50 consecutive patients treated by a new plan in which various procedures used in one place or another during the past twenty years are employed, but potassium chloride is added to the solutions containing sodium chloride, sodium lactate and glucose. In all severely ill patients, blood or plasma infusions are also carried out. Before the institution of this method of therapy the "corrected mortality rate" of 53 consecutive patients had been 32 per cent. It will be of interest to see whether the marked improvement which occurred with the introduction of the new method of therapy is maintained in following years.

SUMMARY

The morbidity and mortality of diarrhea still remain high in Cincinnati. Artificial feeding, poverty, poor sanitary facilities, and ignorance appear at least in part responsible for the high incidence of the disease. Specific infection with dysentery and related bacilli accounts only for a small percentage of cases. Parenteral infection also plays an unimportant role in the causation of severe diarrhea. Compared with previous experience a low death rate has been achieved for the past two years at the Cincinnati General Hospital by the use of consistent, planned, continuous, intravenous therapy. In 292 infants and children admitted to the hospital seriously ill with diarrhea the death rate was 7.6 per cent. Two hundred and twenty-one of these patients were infants under one year of age. Here the death rate was 9.1 per cent. The "corrected case fatality rate" for the series was 5.6 per cent.

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PENICILLIN AS AN AID IN THE TREATMENT OF PRIMARY STAPHYLOCOCCUS PNEUMONIA WITH EMPYEMA

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PRIOR to the advent of penicillin as a therapeutic agent, the reported mortality of staphylococcal infection of the pleural cavity ranged from 22 to 100 per cent. Riley,[1] in 1944, reported fifteen patients treated with sulfonamides, staphylococcal antitoxin, and a bacteriophage, with a mortality of 40 per cent. In a group of twenty-two infants under one year of age treated by various surgical methods, there were eight fatalities (36 per cent), and of seven children over one year of age, two died (28 per cent). Hochberg and Kramer,[2] in 1939, reported thirty-three patients treated by surgical methods with a gross mortality of 22 per cent. Ladd and Swan,[3] in 1943, pointed out the significance of age as a prognostic factor when they reported a mortality of 66 per cent in twelve infants under 4 months of age in contrast to a mortality of 5 per cent in twenty-one children of over 4 months. These patients were treated with surgical methods alone. In 1942, Clemens and Weems reported six cases of primary staphylococcal pneumonia. All of the patients had empyema and four of them had a pyopneumothorax. The mortality was 100 per cent and the authors felt that the overwhelming toxemia was the main factor in the cause of death. A short time ago Philips and Kramer[5] reported five cases of staphylococcal infection of the lung and pleural cavity in infants less than 3 months of age. One patient, moribund on admission, died within eighteen hours, and autopsy showed multiple lung abscesses without evidence of empyema. Of the four who survived, two received both intrapleural and intramuscular penicillin and two received only intrapleural penicillin. Thoracotomy and rib resection were required in two cases. The improvement in mortality was attributed largely to the addition of penicillin to other therapeutic methods.

Between 1929 and 1944, eight children with primary staphylococcal pneumonia and empyema were admitted to Strong Memorial Hospital. Two of these patients (25 per cent) died. Of the remaining six, two were treated by aspiration and trocar drainage only; two others were treated with sulfonamide, aspiration, and staphylococcal antitoxin; two received only multiple aspirations. All recovered. The average period of hospitalization was 38.5 days, the longest admission being 79 days and the shortest, 6 days. Judging from these cases, one might assume that there is a marked variation in the virulence of the infecting organism or a marked variation in the individual immune response. Age did not seem to be an influencing factor.

Seven children with staphylococcal pneumonia and empyema were recently admitted to Strong Memorial Hospital. All were treated by both intrapleural and intramuscular injections of penicillin. In reviewing the literature, it was

noted that reports on this method of treatment of primary staphylococcal pneumonia with empyema in children were relatively scarce. Consequently, it was felt that even though the present series is quite small, a description of the plan of treatment and the results obtained is warranted.

CASE REPORTS

CASE 1.—R. B., an 18-day-old infant, was admitted May 17, 1944, with a chief complaint of fever. Several days after birth she had had mild diarrhea and two episodes of cyanosis. A presumptive diagnosis of congenital heart disease had been made. She had been discharged from the nursery on the eighth day of life in good condition. After that there had been only one episode of cyanosis. Two days before admission the formula was changed and one drop of a 1:1,000 solution of atropine was added to alternate feedings because of hypertonicity and frequent vomiting. The day preceding admission she was irritable, vomited, and choked on her 6 A.M. feeding. In the afternoon she developed a temperature of 103.5° F. She had received one drop of atropine in her 10 A.M. feeding.

Physical examination on admission revealed a well-developed, well-nourished infant, acutely ill with a temperature of 38.5° C. The lungs were clear. The heart was not enlarged but there was a systolic blow over the precordium. The tip of the spleen was palpable and the liver was felt one fingerbreadth below the costal margin.

Laboratory studies on admission showed the following: red blood cells, 3,400,000; hemoglobin, 14.5 Gm.; white blood cells, 13,000, with polymorphonuclears 70 per cent, lymphocytes, 26 per cent, and monocytes, 4 per cent. The urine contained a trace of albumin. Hemolytic *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus viridans* were isolated from the nose and throat. No pneumococci were recovered from the mouse inoculation. In the blood culture, hemolytic *Staphylococcus albus* grew in the broth but not in the plates. Roentgenograms showed no evidence of pneumonia.

Course.—The child received sulfadizine, 0.25 Gm. stat. and 0.125 Gm. every six hours; the fever persisted. On the second hospital day she was cyanotic, and there were râles over the left chest but no dullness to percussion. The following day a flat percussion note with suppression of breath sounds and fine râles was present over the entire left chest. Her condition became worse and she was placed in an oxygen tent. Thoracentesis yielded 0.5 c.c. of serosanguineous fluid, from which hemolytic *Staph. aureus* was isolated. The child's condition improved slowly but she remained febrile. Three transfusions of whole blood were given. The sulfadiazine was discontinued after ten days. On the fifteenth hospital day, thoracentesis yielded 4 c.c. of bloody fluid, culture of which was sterile. The white blood count remained elevated; suppressed breath sounds, tubular breathing, and fine râles persisted over the left chest. On the following day the intramuscular injection of 2,000 units of penicillin every two hours was started and continued for ten days. The temperature dropped to normal and remained so until the child was discharged on June 16, thirty days after admission.

On June 30, 1944, the infant was readmitted with a complaint of gradually increasing cough for six days without fever. Physical examination revealed dullness to percussion, fine râles, and suppressed breath sounds over the left chest. The cardiac murmur had disappeared.

Laboratory studies on admission showed the following: red blood cells, 3,650,000; hemoglobin, 10 Gm.; white blood cells, 21,600 with polymorphonuclears 56 per cent, and lymphocytes 44 per cent. Hemolytic *Staph. aureus* and *Str. viridans* were grown from the nose culture; no pneumococci were recovered from the mouse inoculation. X-ray showed a localized collection of fluid in the left lower chest.

The child remained afebrile throughout. On the day of admission, 30 c.c. of thick green pus were aspirated from the left chest and 10,000 units of penicillin were injected into the empyema space. Hemolytic *Staph. aureus* was cultured from the pus. The next day, 3 c.c. of pus were aspirated, and 5,000 units of penicillin were injected. On the next five successive days, no fluid was obtained on thoracentesis. During the first twenty-four hospital days, 2,000 units of penicillin were injected intramuscularly every three hours, and two transfusions of whole blood were given. X-rays of the chest seven days and twenty-four days after admission

showed marked decrease in the size and density of the cavity. The patient was discharged on the twenty-eighth hospital day. X-rays two weeks later showed thickened pleura and accentuated markings at the left base. No fluid was present.

CASE 2.—H. B., an 11-year-old boy, was admitted Jan. 10, 1945, with chest pain, fever, and loss of appetite. Six days before admission he had a sore throat, chest pain, difficulty in breathing, and a cough productive of mucoid sputum which was not blood tinged. He was nauseated and vomited several times. His physician diagnosed pleurisy and prescribed sulfathiazole, 1.0 Gm. every four hours. Four days before admission the patient noted a generalized erythematous rash and a sore tongue. The next day the sulfathiazole was discontinued and sulfadiazine given. The rash faded rapidly but the chest pain, fever, and anorexia became more marked.

On admission, physical examination showed a well-developed, 11-year-old boy with a temperature of 39.7° C., who was severely ill. His respirations were labored and rapid with an expiratory grunt and splinting of the left chest. There was a profuse, mucopurulent, nasal discharge. The left chest was resonant to percussion above the fourth rib anteriorly and the second rib posteriorly, with a few râles in these areas; below this there was flatness to percussion with absent breath sounds. The right chest was normal. The abdomen was moderately tender in both upper quadrants. The spleen was not palpable.

Laboratory studies on admission showed the following: red blood cells, 4,250,000; hemoglobin, 14.0 Gm.; white blood cells, 12,150; differential smear, polymorphonuclears 69 per cent, lymphocytes 14 per cent, myelocytes 12 per cent, eosinophiles 5 per cent. The urine was normal. Blood sulfadiazine level was 3.3 mg. per 100 c.c. Cultures from the nose and throat yielded *Str. viridans* and a yeast; no pneumococci were recovered from the mouse inoculation. Blood culture was sterile. X-rays of the chest showed a left hydrothorax with no definite area of pneumonic infiltration.

Course.—Thoracentesis yielded 200 c.c. of turbid fluid. Gram stains of the sediment of this fluid showed gram-positive cocci, but the cultures were sterile. The boy was given 1.0 Gm. sulfadiazine every four hours. On the third hospital day, intramuscular injection of 5,000 units of penicillin every three hours was started. This dosage was doubled the next day and eight days later it was increased to 15,000 units every two hours when a favorable response was not apparent. Daily, for fourteen days, 100 to 350 c.c. of turbid straw-colored fluid were removed from the chest and 15,000 units of penicillin were injected. Cultures of the fluid from the fifth and sixth thoracentesis yielded hemolytic *Staph. aureus*, although the smears were negative. Repeated blood cultures during this period were sterile. He continued to run a septic course showing little improvement. Sulfadiazine was discontinued after one week of administration. On the fourteenth thoracentesis, pus was encountered in the seventh interspace in the posterior axillary line immediately after the usual turbid fluid had been obtained one interspace higher. This pus showed many gram-positive cocci on smear and hemolytic *Staph. aureus* on culture. Trocar drainage was instituted, the cavity was irrigated daily, and 15,000 units of penicillin were instilled with the tube clamped off for several hours. Sulfathiazole was given in doses of 1.25 Gm. every four hours; the highest blood level obtained was 8.7 mg. per 100 c.c. Following trocar drainage, the patient's condition improved gradually and he remained afebrile. Local penicillin was discontinued on the twenty-third hospital day and cultures of the empyema fluid were negative three days later. On the forty-eighth day the tube was removed, following which the sinus closed rapidly. The patient showed slight daily temperature elevations when first allowed out of bed, but was well when discharged on the fifty-seventh hospital day. X-rays taken one week later showed the lung fields to be essentially normal with residual adhesive pleuritis at the left base.

CASE 3.—E. K., a 20-month-old white girl, was admitted Jan. 11, 1945, with a chief complaint of abdominal pain. One week before admission she developed an upper respiratory infection characterized by coryza and a nonproductive cough, followed by anorexia. The night before admission she vomited twice and complained of severe, generalized, abdominal pain. On the morning of admission the temperature was 104° F. A physician was called who found tenderness in the right lower quadrant of the abdomen and advised hospitalization.

Physical examination on admission showed a severely ill infant with a temperature of 39.6° C. Her respirations were rapid with an occasional expiratory grunt. There was minimal inspiratory lag on the left side of the chest with dullness to percussion, decreased breath sounds, and fine râles over the left base. The abdomen was not distended but there was slight resistance and tenderness to deep palpation in the right upper quadrant. The spleen was not palpable.

Laboratory studies on admission showed the following: red blood cells, 3,960,000; hemoglobin, 10.3 Gm.; white blood cells, 17,600; polymorphonuclears, 83 per cent and lymphocytes, 17 per cent. Blood culture showed *Staph. albus* in the broth but no growth in the plates. Nose and throat culture yielded no pathogens. Hemolytic *Staph. aureus* was recovered from the mouse inoculation, but no pneumococci were found. A roentgenogram of the chest showed bronchopneumonia at the left base.

Course.—The patient was treated with parenteral fluids and sulfadiazine, 0.250 Gm. every four hours. The following morning the area of dullness at the left base had increased slightly and the temperature remained elevated. On the second hospital day, examination of the chest showed the presence of fluid and this was confirmed by x-ray. Thoracentesis yielded 1 c.c. of fluid which on smear showed occasional gram-positive cocci and on culture grew hemolytic *Staph. aureus* which was coagulase-positive. A transfusion of whole blood was given. On the third hospital day she appeared extremely ill and had labored respirations, and the spleen became palpable. The dosage of sulfadiazine was increased although the level in the blood was 10.8 mg. per 100 c.c. She received fluids by vein and was placed in an oxygen tent. Five days after admission the level of fluid in the chest was higher and two thoracenteses were performed with the removal of 60 c.c. of thick, reddish-brown pus. 20,000 units of penicillin were instilled into the pleural space following each thoracentesis and intramuscular penicillin was begun, 10,000 units for two doses and then 5,000 units every three hours. She was also given plasma and parenteral fluids. Daily thoracenteses were performed with the removal of 15 to 95 c.c. of pus and instillation of 20,000 units of penicillin. Her condition improved gradually and x-rays showed progressive localization of the fluid. Sixteen days after admission trocar drainage was instituted and constant suction applied. The empyema cavity was irrigated frequently with normal saline and Dakin's solution. Three weeks after admission, penicillin and sulfadiazine were discontinued in spite of positive cultures from the pleural fluid as the empyema cavity was well walled off and there was no evidence of an active pneumonic process. Pantopaque injections of the cavity on the thirty-sixth and forty-eighth hospital days showed progressive diminution in its size. Two weeks after chemotherapy was discontinued, cultures of the empyema drainage were sterile. Ten days later, the catheter was removed and the sinus tract closed gradually. Fifty days after admission the sinus tract was entirely healed, and x-rays showed re-expansion of the lungs with clear parenchyma and slight pleural thickening over the left base.

CASE 4.—G. B., a 6-month-old boy, was admitted Feb. 24, 1945, with a chief complaint of fever and grunting respirations. Two weeks before admission he developed an upper respiratory infection and later had a mild cough. The day before entry he vomited once, became irritable, and had fever and grunting respirations.

Physical examination showed a well-developed, well-nourished but pale and acutely ill infant with a temperature of 39.3° C. There was a mucopurulent nasal discharge and the pharynx showed moderate injection. There was slight dullness to percussion at the left base, but no râles or changes in the breath sounds were heard.

Laboratory studies on admission showed the following: red blood cells, 4,500,000; hemoglobin, 14.5 Gm.; white blood cells, 17,000; polymorphonuclears, 91 per cent, lymphocytes, 8 per cent, and monocytes, 1 per cent. Nose and throat cultures yielded *Staph. albus* and *Neisseria catarrhalis*. Blood culture was sterile. X-rays showed a hazy mottled density at the left base and elevation of the left diaphragm.

Course.—The patient was given sulfadiazine, 0.315 Gm. every four hours. He continued to have a spiking fever. Sulfadiazine blood levels were between 13.2 and 15.1 mg. per 100 c.c.

On the third day after admission there was definite splinting of the left chest with flatness to percussion and absent breath sounds. The administration of oxygen and intramuscular injection of penicillin, 10,000 units stat. and 5,000 units every three hours were started. A nose and throat culture showed hemolytic *Staph. aureus.* Thoracentesis yielded 10 c.c. of sanguineous purulent fluid which showed gram-positive cocci on smear. Thoracenteses were performed daily and 15,000 units of penicillin were injected into the pleural space. His condition improved, the respirations became easier, and the temperature returned to normal. Smears and cultures of the pleural fluid continued to show hemolytic *Staph. aureus.* On the thirteenth hospital day, trocar drainage was institute and followed by continuous suction. Fifteen days after admission sulfadiazine was stopped, and two days later the intramuscular injection of penicillin was discontinued. Cultures of the pleural fluid continued to show hemolytic *Staph. aureus.* On the forty-fourth hospital day the local penicillin, which had been discontinued following insertion of the catheter into the chest, was again given for one week. One week later drainage from the cavity was minimal and on pantopaque visualization the cavity was seen to lie posteriorly in the mid-lung zone with normal surrounding parenchyma. On the fifty-fourth day the child's temperature rose and considerable purulent material was aspirated from the chest which yielded hemolytic *Staph. aureus* on culture. Also at this time bilateral myringotomy was performed because of tense, injected drums. Local penicillin and oral sulfadiazine were reinstituted and continued for one week. Two days after these were discontinued the catheter slipped out and was not replaced. The sinus closed rapidly and there was no drainage five days later. At this time the area occupied by the empyema cavity was clear except for increased lung markings and thickened pleura. He was discharged on the sixty-seventh hospital day, and two weeks later x-ray revealed only slight pleural thickening.

CASE 5.—S. W., a 2½-year-old girl, was admitted Feb. 27, 1945, referred with a diagnosis of "pneumonia or appendicitis." One week before admission she developed croup which responded well to sulfadiazine. The day before admission she again had fever, became restless, and had grunting respirations. Sulfadiazine was given, and she received a total of 1.75 Gm. without improvement. On the morning of admission she developed moderately severe abdominal pain without nausea, vomiting, or diarrhea.

Physical examination on admission revealed a well-nourished, acutely ill child with a temperature of 39.3° C. Her skin was hot and dry. She had a profuse purulent nasal discharge and exudate on the tonsils.

Her respirations were irregular and grunting. The percussion note over the right base posteriorly was flat and there was suppression of breath sounds with many fine râles heard over this area. There was voluntary spasm and tenderness to palpation in the right upper quadrant of the abdomen.

Laboratory studies on admission showed the following: red blood cells, 5,360,000; hemoglobin; 14.5 Gm.; white blood cells, 18,650, with polymorphonuclears, 84 per cent, lymphocytes, 14 per cent, and monocytes, 1 per cent. Hemolytic *Staph. aureus* and pneumococci types IV and VI were cultured from the throat. The blood culture was sterile. The blood sulfadiazine level on admission was 10.1 mg. per 100 c.c. X-ray of the chest showed a pneumonic consolidation at the right base.

Course.—She received sulfadiazine, 1.95 Gm. per day, and parenteral fluids. The next day she was cyanotic during coughing spells. Her temperature remained elevated. There was an increase in the amount of consolidation in the right lower lobe and a small pleural effusion was present. Penicillin, 7,500 units, was then administered every three hours. Thoracentesis on the right yielded 40 c.c. of thick pus from which hemolytic *Staph. aureus* was cultured. 20,000 units of penicillin were instilled into the pleural cavity. Following this, the empyema cleared rapidly. Two days after admission, 15 c.c. of pus were obtained on thoracentesis, and the following day, 3 c.c.; both times, cultures yielded hemolytic *Staph. aureus.* Penicillin was given intrapleurally with each thoracentesis. Nine days after admission no fluid was obtained from the chest. Her improvement after the first week was steady and rapid. She was discharged three and one-half weeks after admission. X-rays showed only residual pleural thickening.

CASE 6.—R. A., a 2-month-old, white male, was admitted on April 15, 1945, with a chief complaint of a cough and cold. He was apparently well until the day before admission, when he developed a mild cough. On the day of admission he developed rapid respirations and refused his food. A twin brother was said to be in good health.

Physical examination on admission showed a well-developed baby with a temperature of 36.5° C. and with rapid, shallow, gasping respirations. His skin was icteric and cold. The extremities were cyanotic and the fontanelle was slightly depressed. The chest showed a lag on the right side with suprasternal retractions. There was flatness to percussion over the right base and in the axilla. Fine, moist, crackling râles were heard over both lung fields, but were more marked on the right. The liver was felt one fingerbreadth below the costal margin and the spleen, two fingerbreaths.

Laboratory studies on admission showed the following: red blood cells, 2,400,000; hemoglobin, 8.5 Gm.; white blood cells, 22,300, with polymorphonuclears, 44 per cent, lymphocytes, 44 per cent, monocytes, 3 per cent, and juvenile forms, 9 per cent. Blood culture was sterile. A nose and throat culture revealed a predominance of hemolytic *Staph. aureus;* no pneumococci were recovered from the mouse inoculation. X-ray revealed compensatory emphysema of the left lung, poor aeration of the right lung with prominent root markings, and many small parenchymal infiltrations. No fluid was visualized.

Course.—The patient received 15,000 units of penicillin intramuscularly, immediately followed by 5,000 units every three hours, 0.25 Gm. of sodium sulfadiazine intravenously, and 0.25 Gm. every six hours thereafter by mouth. He received parenteral fluids including hypertonic glucose and whole blood, and was placed in an oxygen tent. Three hours after admission he became apneic but rallied after receiving caffeine sodium benzoate and artificial respiration. During the next twenty-four hours his color improved slightly but his temperature rose to a maximum of 40.2° C. and was only slightly lowered by aspirin and tepid sponges. He then developed abdominal distention and accentuated respiratory difficulty. His course continued steadily downhill and despite restorative measures he expired thirty-six hours after admission.

At autopsy the left pleural cavity contained a trace of clear, straw-colored fluid, and the parietal surfaces were clear. The right pleural cavity contained approximtely 10 c.c. of thick, dark, purulent fluid. The left lung was of normal size; the upper lobe was emphysematous, while the lower lobe contained a large, firm, consolidated area which on section had a reddish gray color and showed a few small abscesses filled with creamy pus. The surface of the right lung showed many small, blisterlike areas filled with creamy, yellow pus, and the bronchi were reddened and filled with exudate. The lung sank quickly in water and was extensively consolidated in all areas. Microscopically, the heavily consolidated areas showed white cells and fibrin in the alveoli and bronchi with severe necrotization, abscess formation, and some hemorrhage. Over these areas there was a thick fibrinopurulent pleural exudate with many bacteria. Smears of the pus and empyema fluid showed many gram-positive cocci in clusters, and cultures were positive for hemolytic *Staph. aureus.* The diagnosis of empyema was not made during life.

CASE 7.—S. K., a 31-month-old boy, was admitted July 19, 1945, with a chief complaint of heavy breathing. Ten days before admission he developed a cough and cold without fever. On the day preceding admission his respirations became labored and grunting, his temperature rose to 103° F., and he took fluids poorly. On the morning of admission he was taken to another hospital where an x-ray of the chest was taken and interpreted as negative. His white count was 10,000. An unsuccessful lumbar puncture was attempted because of a slightly stiff neck. He was sent home and given sulfadiazine, receiving a total of 1.0 Gm. before admission. Late in the evening he suddenly became cyanotic after administration of his medication and was brought immediately to the hospital.

Examination on admission showed an acutely ill 31-month-old child with a temperature of 39.2° C. His respirations were rapid and shallow with an expiratory grunt. There was minimal subcostal retraction without lag or splinting of the chest. The lungs were resonant to percussion with slightly decreased breath sounds over the right lower lobe and loud, harsh

breath sounds over the left lower lung field, without râles. The abdomen was slightly distended but otherwise normal.

Laboratory studies on admission showed the following: red blood cells, 4,500,000; hemoglobin, 12.1 Gm.; white blood cells, 19,200, with polymorphonuclears, 65 per cent, lymphocytes, 31 per cent, monocytes, 2 per cent eosinophiles, 1 per cent, and basophiles, 1 per cent. The sulfadiazine level of the blood was 6.0 mg. per 100 c.c. Nose and throat cultures showed hemolytic *Staph. aureus;* no pneumococci were recovered from the mouse inoculation. X-ray revealed conglomerate shadows in the left lower lung which were interpreted as early bronchopneumonia.

Course.—The patient received parenteral fluids and sulfadiazine, 1.25 Gm. per day. On the morning after admission, because of the continued high fever, the progression of signs in the lung, and the finding of hemolytic *Staph. aureus* in the nose and throat cultures, penicillin was started and the patient was placed in an oxygen tent. Two days after admission the respiratory embarrassment was more marked and there was definite evidence of fluid in the left chest. X-ray showed fluid to the level of the fifth rib posteriorly and increased density in the lung fields, due partly to overlying fluid and partly to definite parenchymal infiltration. Two thoracenteses were performed on the second hospital day with the removal of thick, purulent fluid and instillation of 15,000 units of penicillin into the cavity. Progressively smaller amounts of empyema fluid were removed each day. Penicillin was instilled into the pleural cavity following each thoracentesis. He also received 10,000 units of penicillin every three hours intramuscularly. Supportive measures consisted of several transfusions of whole blood and parenteral Vitamin B complex. On the nineteenth hospital day, cultures of the thoracentesis fluid showed no growth although occasional cocci were seen on three subsequent smears. On the sixteenth hospital day intramuscular penicillin was discontinued but was started again thirty-six hours later because of the presence of a shadow in the left upper lung suggesting pneumonic infiltration, and was continued for sixteen days. On the seventeenth hospital day no fluid was obtained upon thoracentesis and further taps were not done. The patient was discharged thirty-seven days after admission, afebrile and in excellent condition. The X-ray at this time showed slight, residual, pleural thickening at the left base.

COMMENT

It is evident that the plan of therapy varied considerably between the times the first and last cases were treated. Case 1 received relatively small doses of penicillin for rather short periods. Only on the second admission was it given intrapleurally. Case 7 was given larger doses for a longer period. It is now thought that 15,000 to 25,000 units should be given intramuscularly every three hours, even to infants, and that larger doses are probably unnecessary. A thoracentesis should be done each day, as much fluid should be removed as possible, and from 30,000 to 50,000 units of penicillin should be instilled. For older children as much as 50,000 to 75,000 units should be given intrapleurally each day. As Cooke and Goldring[17] have shown, high levels can be maintained in the pleural fluid by giving penicillin once daily into the pleural space and every 3 hours intramuscularly.

Cultures of the pleural fluid rapidly become "sterile" although smears continue to show gram-positive cocci for a varying length of time. One should not be led into a false sense of security by such "sterile" cultures, but rather should make daily smears and continue the administration of both intrapleural and intramuscular penicillin for at least one to two weeks after organisms can no longer be found by smear. It may be discontinued then unless there is further indication for continued administration.

Sulfonamide therapy should be instituted as soon as possible and blood levels of 12 to 15 mg. per cubic centimeter should be maintained. Several observers[18-20] have pointed out a synergistic action when sulfonamides and penicillin are given together, although others[21] do not agree with this.

Frequent small blood transfusions during the acute stages are beneficial as most infants have a moderately severe anemia with the infection. They are also of value in that they furnish fresh complement. It has been shown that infants normally have low titers of complement and also that the titer drops during acute infections.

Additional supportive therapy includes the maintenance of an adequate intake of food, fluids, and vitamins, especially members of the B complex. Oxygen should be administered when necessary.

In some instances various surgical procedures must be performed. Cases in which this becomes necessary are those in which loculation has occurred and isolated pockets of pus have formed. All of these are not accessible to the needle or to chemotherapy, and surgical drainage may have to be employed. This localization was exemplified in Case 2 where an isolated pocket was encountered on the fourteenth thoracentesis. When the fluid continues to accumulate, and cultures or smears remain positive, trocar drainage with constant or intermittent suction, and irrigation with Dakin's or some other suitable solution may be required.

All cases should be followed closely by x-ray and fluoroscopy and by repeated physical examination. One should watch for other foci of staphylococcal infection.

CONCLUSION

1. Seven cases of primary staphylococcal pneumonia with empyema are presented. The mortality rate was 14 per cent; the infant who expired, died thirty-six hours after admission.

2. Treatment consisted of the administration of relatively large doses of penicillin intramuscularly and directly into the pleural space, and of moderately large amounts of sulfonamide by mouth. Supportive treatment included blood transfusions and maintenance of a good state of nutrition.

3. Patients should be followed closely by x-ray and fluoroscopy and by repeated physical examination. Surgical drainage should be instituted when indicated.

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THE A-B BLOOD GROUPS AND Rh-Hr BLOOD TYPES IN CONGENITAL ATHETOSIS

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ONE of the syndromes attributed to defects of the basal ganglia is congenital athetosis. The etiology of this condition is generally obscure, but recent studies in a group of athetotic patients with kernicterus have clarified the mechanism.

Kernicterus occurs almost exclusively in patients who have had icterus gravis,[1-4] a severe and highly fatal antigen-antibody disease,[6] during the neonatal born period. This condition is probably brought about by intravascular agglutination or conglutination,[4, 5] often associated with intravascular hemolysis of the infant's red blood cells by an antibody which is manufactured by the mother and is transferred across the placental membrane to the infant. While sensitization of an Rh-negative woman by an Rh-positive fetus accounts for the bulk of the cases,[6] sensitization to the A-B factors can also give rise to the disease.[4]

There is evidence that the bile staining of the basal ganglia (hence the name kernicterus) is secondary to cellular injury and that the pigmentation occurs in the same way that intravital dyes generally localize in zones of injury.[2, 4, 5]

In order to determine whether or not isosensitization might explain other instances of congenital athetosis, the various blood factors (A, B, M, N, Rh, Hr) were studied in a group of children with this condition. Where the mother's blood belonged to type rh* (Rh negative), studies of her blood serum were made for agglutinins and glutinins against Rh-positive cells.†

The group studied consisted of twenty-three children with athetosis beginning early in life. The cases were assembled at the Institute for Crippled and Disabled Children, New York, and at the Ridgewood Branch of Hackensack Hospital Orthopedic Clinic, through the courtesy and kind cooperation of Dr. George Deaver to whom we wish to express our appreciation. The patients ranged from 1 to 26 years of age, nine being male and fourteen female. Labor was difficult in fifteen of twenty-three cases; in two it was precipitate, in four it was premature, and in three it was normal. There were three twin births. The postnatal course was stormy in thirteen cases, normal in nine, and in one the mother was unable to tell whether or not there were any difficulties. The most common postnatal symptom was cyanosis (eight cases); next in frequency was convulsions (seven cases).

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*Type rh blood gives negative reactions in tests with all three Rh antisera, anti-Rh$_0$, anti-Rh′, and anti-Rh″.[7]

†For the technique of the Rh sensitization tests, see Wiener.[8]

Intelligence quotients were determined in ten of the older children, and the scores ranged from 55 to 114. One girl (not tested) was going to college. Three children aged 2, 5, and 9 years were severely retarded. The remainder appeared to be within the normal range. Estimates of intelligence in children with athetosis are probably too low, because the children have great difficulty in expressing themselves. Moreover, their early training is apt to have been inadequate.

The results of the study are shown in Table I. In only five of the twenty-three mothers was the blood Rh negative, and in none of these were anti-Rh agglutinins or glutinins found in their serum. With regard to the Landsteiner blood groups, in four instances (Cases 6, 14, 15, and 18) the blood group of the patient was incompatible with the mother's blood group. While the maternal alpha and beta isoagglutinins in these cases were not titrated, this incidence of incompatibility (17 per cent) is less than that occurring in normal families (about 25 per cent),[9] and it is, therefore, unlikely that the A-B factors had any bearing on the occurrence of athetosis in our series of cases.

TABLE I. BLOOD GROUPS AND Rh-Hr TYPES IN TWENTY-THREE PATIENTS WITH CONGENITAL ATHETOSIS

			MOTHER			PATIENT		
CASE	AGE (YR.)	SEX	GROUP AND SUB-GROUP	M-N TYPE*	Rh-Hr TYPE†	GROUP AND SUB-GROUP	M-N TYPE	Rh-Hr TYPE
1	20	F	A_1B	M	Rh_2	B	M	rh
2	16	M	A_1	MN	rh	O	MN	rh
3	19	F	A_1	MN	rh	A_1	M	Rh_1rh
4	20	F	A_2B	M	Rh_1rh	B	MN	Rh_1rh
5	26	M	B	MN	Rh_2	B	MN	Rh_2
6	17	F	O	MN	Rh_1Rh_2	A_1	MN	Rh_1Rh_2
7	22	M	B	M	Rh_1Rh_1	O	M	Rh_1Rh_1
8	16	F	A_1	MN	Rh_1Rh_1	A_1	M	Rh_1Rh_1
9	17	F	O	MN	rh	O	N	rh
10	20	F	A_1	M	Rh_1rh	A_1	MN	rh
11	18	F	O	M	Rh_1Rh_1	O	M	Rh_1Rh_2
12	2	F	O	N	Rh_1Rh_1	O	N	Rh_1Rh_1
13	3	F	A_1	MN	Rh_1rh	A_1	MN	rh
14	2	M	O	MN	rh	A_1	N	Rh_1rh
15	9	F	B	MN	Rh_1Rh_1	A_2	M	Rh_1Rh_2
16	3	F	A_2	M	Rh_2	O	MN	Rh_2
17	2	F	A_1	M	Rh_1rh	O	M	Rh_1rh
18	3	M	O	N	Rh_1rh	A_1	MN	Rh_1rh
19	1	F	O	M	Rh_1Rh_2	O	M	Rh_1rh
20	5	M	B	MN	Rh_1rh	B	MN	Rh_1rh
21	3	M	A_1	M	rh	A_1	M	Rh_1rh
22	3	M	O	MN	Rh_1rh	O	MN	Rh_1rh
23	4	M	O	M	Rh_1rb	O	M	Rh_1rh

*The M-N types are not important clinically, but are included for the sake of completeness.
†For nomenclature, see Wiener and associates.[7]

The failure of isosensitization to explain the etiology of the bulk of cases of congenital athetosis is to be expected from the case histories and the neurological examinations. In patients with kernicterus there is usually a history of anemia and jaundice in the neonatal period, requiring treatment with repeated transfusions. This is not an invariable rule, however. In some instances the disturbances in the newborn period may be so slight as not to

require even a single transfusion. Convulsions, somnolence, and stupor during the newborn period are common to all athetotics and hence are of no value in differentiating kernicterus from the group as a whole. In kernicterus there is generally severe mental retardation, while in the ordinary athetotic the intelligence is apt to be good. A further differential feature is the health of the subsequent siblings. When a mother has had a child with icterus gravis, subsequent children are invariably erythroblastotic, unless the child happens to be Rh negative like the mother. In the present series, ten mothers had seventeen children after the birth of the affected children. None of the offspring showed erythroblastosis during the neonatal period and none had athetosis.

SUMMARY AND CONCLUSIONS

1. The Rh factors were determined in twenty-three patients with congenital athetosis in order to discover whether icterus gravis during the newborn period is an etiologic factor. In only five of the twenty-three patients were the mother's red blood cells Rh negative and in none of these were anti-Rh agglutinins or glutinins found in the mother's serum.

2. The A-B blood group of only four of twenty-three of the patients was incompatible with the maternal serum, an incidence of 17 per cent, which is less than the incidence of incompatibility (25 per cent) found in normal families.

3. These results rule out the Rh and A-B factors as etiologic agents in the bulk of patients with congenital athetosis.

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FOLLOW-UP STUDY IN RHEUMATIC SUBJECTS PREVIOUSLY TREATED WITH PROPHYLACTIC SULFANILAMIDE

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THE value of sulfonamide prophylaxis in preventing recurrences of active rheumatic fever has been reported by various clinics since 1939. It is important to know also the subsequent course in rheumatic subjects who, having received prophylactic sulfonamide for various periods of time, are observed throughout several years after treatment has been stopped. Some relevant questions on such prophylaxis still need further analysis, such as which age groups and types of rheumatic individuals should best be protected by prophylactic sulfonamide and the length of time this treatment should be maintained.

It was felt that a follow-up study to observe a group of previously treated individuals would be of value. The following report deals with such a follow-up study carried out from 1941 to 1946 in rheumatic individuals all of whom had previously received sulfanilamide prophylaxis while under the care of the Bellevue Children's and Adolescents' Cardiac Clinics between 1939 and 1943. To date, a total of 109 individuals have been treated with sulfanilamide or sulfadiazine in these clinics, forty-five of these are still continuing sulfadiazine. Several patients have moved too far away for continued observation. Of the remaining individuals, sulfanilamide treatment was terminated in the group who are included in this study, allowing an opportunity for making the follow-up observations.

GROUP STUDIED AND OBSERVATIONS MADE

The follow-up group included fifty-five individuals who were observed throughout a total of 174 patient-years. Seven patients were followed for five years, twenty-two patients for four years, nine patients for three years, seven for two years, and ten for one year. These patients were all personally followed in the clinic at from two- to three-month intervals and more frequently either in the clinic or the hospital when actual or suspected rheumatic activity was noted.

During the 174 patient-years of observation, thirty-nine individuals had no rheumatic recurrences while sixteen developed active rheumatic fever. This represented 158 inactive patient-years in contrast to 16 active patient-years. Of these sixteen cases of rheumatic activity, eight developed in the first year, six in the second year, and two in the third year after prophylactic sulfanilamide had been stopped.

Distribution of years of observation, number and time of recurrences, and length of previous treatment are summarized in Table I. The group of patients who remained free of recurrences and those who developed rheumatic

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activity are compared in respect to factors considered effective in the recurrence pattern of rheumatic fever: past rheumatic history, numbers and severity of attacks, and cardiac diagnoses (Table II); years since last attack (Table III); and ages during the follow-up period (Table IV).

TABLE I. NUMBER AND TIME OF RHEUMATIC RECURRENCES IN RELATION TO YEARS OF PREVIOUS PROPHYLAXIS

	TOTAL	NUMBER OF YEARS OF PREVIOUS PROPHYLAXIS		
		1 YEAR	2 YEARS	3 YEARS
Number of patients	55	22	25	8
Number followed throughout				
5 years	7	6	1	–
4 years	22	8	14	–
3 years	9	3	2	4
2 years	7	1	2	4
1 year	10	4	6	–
Total patient-years of follow-up	174	77	77	20
Number rheumatic recurrences	16	7	4	5*
Year recurrences occurred after stopping therapy				
First year	8	4	3	1
Second year	6	3	1	2
Third year	2	–	–	2

*Three of these 5 cases had each had three or more attacks of severe carditis, with congestive failure in two instances, prior to the years of prophylactic sulfanilamide.

TABLE II. PAST RHEUMATIC HISTORY AND CARDIAC DIAGNOSIS

	INACTIVE GROUP	ACTIVE GROUP
Total number of patients	39	16
Past rheumatic history		
Total number of attacks	100	44
Per cent of total number of attacks		
Chorea	28%	11%
Polyarthritis, minimal carditis	25%	19%
Moderate to severe carditis ± polyarthritis	47%	70%*
Cardiac diagnoses.†—Per cent of inactive and active groups		
Possible and potential heart disease	30.6%	25.0%
Enlarged heart, mitral insufficiency	13.1%	12.5%
Enlarged heart, mitral insufficiency, mitral stenosis	35.7%	12.5%
Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency	15.5%	16.7%
Enlarged heart, mitral insufficiency, mitral stenosis, aortic insufficiency, aortic stenosis	5.1%	31.3%

*Congestive failure had been present in two attacks.

†Diagnoses were made according to the Criteria for the Classification and Diagnosis of Heart Disease by the Heart Committee of the New York Tuberculosis and Health Association.

TABLE III. YEARS SINCE LAST ATTACK OF RHEUMATIC FEVER DURING FOLLOW-UP PERIOD

YEARS SINCE LAST ATTACK	PATIENT-YEARS OBSERVED			
	TOTAL	INACTIVE YEARS (NO.)	ACTIVE YEARS	
			NO.	% TOTAL PATIENT-YEARS
Over 1	13	10	3	23.0
2	31	26	5	16.1
3	36	32	4	11.1
4	40	37	3	7.5
5	30	29	1	3.3
6	13	13	–	–
7	11	11	–	–
Total	174	158	16	

TABLE IV. AGES DURING FOLLOW-UP PERIOD

AGES	PATIENT-YEARS OBSERVED			
	TOTAL	INACTIVE YEARS (NO.)	ACTIVE YEARS	
			NO.	% TOTAL PATIENT-YEARS
9 through 13 years	46	39	7	15.2%
14 through 18 years	108	100	8	7.4%
19 through 22 years	20	19	1	5.0%
Total	174	158	16	

DISCUSSION

The course in fifty-five rheumatic subjects who had remained free of rheumatic activity while taking prophylactic sulfanilamide for one to three years has been observed after this therapy was stopped throughout one to five years. Although the total data obtained in a group of this size are somewhat limited from a statistical point of view and would not justify drawing final or complete conclusions, the record of the follow-up period and the analysis of these data are sufficiently significant and of clinical interest to warrant presentation at this time.

The average recurrence rate in the 174 patient-years observed during the follow-up period was 9.7 per cent. Taking into account the rheumatic susceptibility factors represented in the group studied, this relatively low rate suggests that the period of inactivity and normal health maintained while taking prophylactic chemotherapy may have beneficially altered the rheumatic course. Considerably longer periods of follow-up in cases who have been treated, and comparison with matched cases who have never received treatment, will be essential to establish this point.

There was a lower recurrence rate in patients treated for two years (5.2 per cent) than for those treated for one year (9.1 per cent). These two groups were comparable in respect to rheumatic susceptibility and were followed throughout a coincidentally equal number of follow-up years. At first glance, the results in the group of eight patients that had been treated for three years is both startling and alarming unless analyzed in respect to the types of cases represented in that group. With one exception, because of past history of unusually frequent and severe attacks of rheumatic carditis, therapy had been extended deliberately in these cases. This factor of a higher susceptibility risk must be taken into account in the interpretation of the larger proportion of recurrences in this group. It is interesting and possibly significant, following the longer period of inactivity during three years of prophylactic treatment, that the subsequent recurrences should be distributed over later time intervals after stopping therapy than in the groups treated for shorter periods of time.

It has been frequently questioned whether there might not be danger of increased susceptibility to streptococcal infection and rheumatic recurrences on withdrawal of long-term sulfonamide prophylaxis. Evidence of such a proposed type of risk was not found in this particular group either by the general recurrence rate or by the fact that half of the recurrences did not develop until the second and third years after cessation of treatment.

The observed recurrences were analyzed in relation to those factors established as being effective in rheumatic susceptibility. The influences in the pattern of recurrences of age, type of past rheumatic history, and recency of activity continued to be evident during the follow-up period. The higher percentages of recurrences developed in the younger age-groups and in those who, prior to treatment, had had the more severe types of rheumatic episodes. With increasing time intervals since the last attack there was a progressive fall in the percentage incidence of active years in patient-years observed. Ninety-four per cent of the recurrences developed after the first year and within the fifth year of the last rheumatic episode.

To postulate an answer to the question as to how much benefit might have been obtained by further prophylactic treatment in this group had it not been terminated with observation of their subsequent course, an analysis was made of the results in prophylactic treatment years observed during the same period of time covered in the follow-up study. Possible effect from variation in the amount of rheumatic activity that occurs from year to year is thus eliminated in the comparison of time intervals concomitantly observed. Two reports have been made from the Bellevue Children's and Adolescents' Cardiac Clinics on the results in patients taking sulfanilamide (1939 to 1943, 181 patient-years) and sulfadiazine (1943 to 1945, eighty-seven patient-years) as a prophylactic measure. A further forty-five patient-years on sulfadiazine were observed from 1945 to 1946. Those years of treatment observed from 1941 to 1946 (the period of the follow-up study), and the group of patients then treated, were analyzed. It was found that the treated group was comparable to the follow-up group in rheumatic susceptibility in respect to past rheumatic history and recency of last attack, but that a higher proportion of the younger and presumably more susceptible ages were represented in the treatment years. There were four rheumatic recurrences during 233 patient-years of treatment, the average recurrence rate being 1.7 per cent. (In contrast there are the sixteen recurrences during 174 patient-years of follow-up with the average recurrence rate of 9.7 per cent.) It appears more than likely from the various observations given that further treatment would have been beneficial, particularly in those members of the follow-up group in whom younger age, recency of attack, and severe past rheumatic history represented a higher risk of recurrence.

Reports from a considerable number of clinics agree that sulfonamide has proved a valuable means of preventing rheumatic recurrences. The use of sulfonamide, however, is certainly not without possible dangers, and its prolonged administration requires more supervision and the maintenance of regular cooperation from the patient. Indiscriminate and indefinite use of such chemoprophylaxis in all rheumatic children and adolescents is both unwarranted and impractical either in clinic or private practice.

Decision as to which patients should best be protected by prophylactic treatment would appear to be based most wisely on an evaluation of the various recurrence risks in the individual case. Such factors as the following should be weighed: the higher risk of recurrences in the childhood and early

adolescent years, the fact that relapses appear most frequently in the years immediately following a rheumatic attack, and the higher incidence and greater danger of recurrences in those who previously suffered most frequent or severe attacks of rheumatic carditis. Where the risk is high for one or more of these reasons, it is suggested from observations made in this follow-up study that treatment be sufficiently prolonged to allow the opportunity for maintaining inactivity until adolescence has been reached or for a period of five years since the last attack in children or adolescents who have had repeated or severe episodes of rheumatic carditis.

SUMMARY

1. The course in fifty-five rheumatic subjects who had remained free of rheumatic activity while taking prophylactic sulfanilamide for one to three years has been observed after this therapy was stopped throughout one to five years, for a total of 174 patient-years.

2. The recurrence rate of active rheumatic fever was 9.7 per cent during the follow-up period. Patients who remained inactive and those who developed activity are analyzed in respect to length of treatment and data relevant to susceptibility factors.

3. In this group, there was no evidence of increased susceptibility to streptococcal infections and rheumatic activity at the time sulfanilamide was withdrawn.

4. Suggestions are made as to the types of patients probably best treated and the length of time treatment may be advisable in the various types.

Appreciation is expressed for the great help rendered by Miss Marie Summit, social worker for the Bellevue Children's and Adolescents' Clinics, whose untiring efforts made such a follow-up study possible.

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SPOTTED FEVER TREATED WITH PARA-AMINOBENZOIC ACID

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FOR the past few years it has been known that the chemotherapeutic agent para-aminobenzoic acid effectively reduced the mortality from experimental murine typhus in white mice. This was proved by Snyder, and associates.[1] This agent has inhibited also the growth of epidemic and murine typhus rickettsias in the developing hen's egg, thereby prolonging the survival time of infected chick embryos, in the experiments of Hamilton and associates.[2] This experimental work indicated that para-aminobenzoic acid did not exercise a direct lethal action on the rickettsias, but in some way interfered with their growth and proliferation within tissue cells. It was thought that this action was due to a modification of enzymes as yet unidentified. Only the para form of this acid was effective.

Yoemans and associates[3] studied the therapeutic effect of this agent on human louse-borne typhus in Cairo, Egypt. Their results indicated that this disease was greatly modified, provided the drug was given early in the illness. Large doses, 24 to 28 Gm., were administered orally in twenty-four hours, and blood concentrations between 10 and 20 mg. were obtained. They experienced no toxic reaction other than temporary lowering of the white blood cell count in a few cases.

Appreciating the fact that para-aminobenzoic acid may be of value in other rickettsial diseases, Rose and associates[4] used it very effectively in one case of a white woman, aged 46, suffering with Rocky Mountain spotted fever. They administered 4 Gm. initially and then 2 Gm. in 25 c.c. of chilled 5 per cent sodium bicarbonate solution every two hours. The treatment was continued for four days with blood levels ranging from 6.6 to 18.6 mg. per cent. Their results were very gratifying in that the patient made a prompt and uneventful recovery. Following their suggested plan of treatment, a 4-year-old child infected with spotted fever was effectively treated in Grandview Hospital, Sellersville, Pa.

CASE REPORT

L. B., a white female child 4 years of age, was admitted to Grandview Hospital July 17, 1946, complaining of fever, chills, vague pain in joints, and sore throat. On admission, her temperature was 101.2° F., pulse 130, and respiration 30. July 10, 1946, one week before admission to the hospital, the child developed a mild sore throat followed by fever and intermittent pains in various joints of her body. She continued to have daily elevations in temperature, and on July 15 a papular rash developed on the thorax. On this same day the child began to complain of abdominal pain, and a soft systolic murmur was heard at the apex. The attending physician suspected rheumatic fever and for such she was treated. When she failed to respond to salicylate therapy and bed rest, she was admitted to Grandview Hospital, where a tentative diagnosis of spotted fever was made. The mother was again carefully interrogated and related that on June 30, 1946, she had taken the child on a picnic. Upon returning home she removed a tick from the child's underwear. It was

not attached to the skin nor could she find any evidence of a bite. Unfortunately, she did not give this history to the attending physician on previous questioning, as she had considered it of no importance.

Physical examination revealed a thin, pallid, female child, manifesting evidence of toxicity and drowsiness. The skin was covered with a generalized papular rash and small petechial spots were visible on the hands. There was generalized adenopathy. The pharynx was slightly injected. There were no abnormal findings in the lungs. The heart was rapid but not enlarged and a soft grade 2 systolic murmur was heard at the apex. The liver was tender and enlarged two fingerbreadths below the costal margin. No other abdominal organs were palpable. The extremities were negative except for the papular rash. All reflexes were normal. Examination of the eye grounds revealed no abnormal findings. The laboratory findings during her stay in the hospital are given in Chart II.

CHART I. TEMPERATURE

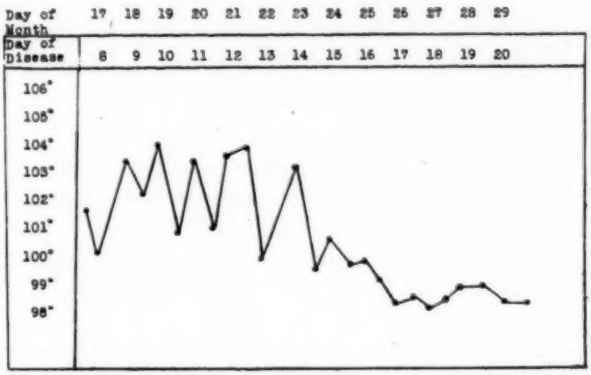

CHART II. LABORATORY FINDINGS*

DATE	URINE	PAB† BLOOD LEVELS	AGGLUTINATION AND OTHER TESTS, ETC.	BLOOD STUDIES
7/17	2 albumin; hyaline and granular casts 30-35/1pf; W.B.C., 2-3/hpf		Typhoid O, negative Typhoid H, negative Paratyphoid A, negative Paratyphoid B, negative *B. Abortus* negative Proteus OX-19, positive 1:40	Hb., 11.5 Gm. %; R.B.C. 3,960,000; W.B.C. 7,900, polymorphonuclears, 57%, monocytes, 2%, lymphocytes, 41%; sedimentation rate, 19 mm. in 60 min.
7/18				Blood culture taken
7/20	2 albumin; hyaline and granular casts occasional; W.B.C., 6-8/hpf; R.B.C. occasional			Blood culture negative
7/22		8.8 mg. %	Proteus OX-19, positive 1:640	W.B.C. 12,700; blood culture negative
7/23		None present	Heterophile antibody reaction negative	W.B.C. 12,500; blood culture negative
7/25	W.B.C., 3-4/hpf	6 mg. %		W.B.C. 8,100
7/26			Proteus OX-19, positive 1:640	Blood culture negative

*On July 24, serum from the patient was sent to Dr. Charles Armstrong, Division of Infectious Disease, U. S. Public Health Service, Bethesda, Maryland. The following results were reported: complement fixation tests: endemic typhus, negative; Rocky Mountain spotted fever, positive 1:512, agglutination test: *B. proteus* OX-19, positive 1:1280.

†PAB para-aminobenzoic acid.

Treatment.—As soon as a positive diagnosis of Rocky Mountain spotted fever was established, para-aminobenzoic acid was administered, the initial dose being 4 Gm. followed by ½ Gm. every hour with 5 c.c. of 5 per cent solution of sodium bicarbonate. There was no nausea. The frequency of administration was deemed necessary because of the rapid elimination of this drug. We encountered great difficulty in obtaining an adequate supply of the acid, and on July 23 none was available. It was on this day that her blood concentration was zero and her temperature rose to 103° F. Late in the evening of July 23, more of the drug was procured and another initial dose of 4 Gm. was given. For the following two days she again was given ½ Gm. every hour. The drug was discontinued on July 25. A total of 30 Gm. had been administered.

Within twenty-four hours after the drug was started, the child showed remarkable improvement; she became more alert and talkative, ate well without help, and sat up in bed playing with her toys. The omission of the drug on July 23 did not seem to have any unfavorable effect except for the rise in temperature. After that date her temperature returned to normal and her condition improved rapidly. Recovery was uneventful and she was discharged from the hospital on July 29. By this time the rash had completely disappeared and only small discolored areas remained.

COMMENT

As confirmed by laboratory tests, history of a tick bite, and typical clinical manifestations, this child undoubtedly suffered from Rocky Mountain spotted fever. Para-aminobenzoic acid effectively produced a decrease in temperature and rapid improvement in the child's well-being. It is to be noted that the high blood concentration as suggested by Rose and associates[4] was never obtained, but in spite of this the clinical course, after administration of the drug, was one of prompt recovery.

It is interesting to note the ease in which the early stages of this disease might be confused with rheumatic fever. This child had many of the typical symptoms of rheumatic fever in the early days of her disease, sore throat, joint pains, abdominal pain, and a heart murmur. Since some cases of rheumatic fever develop a skin rash, this finding would only add to the confusion. The fact that the history of exposure to a tick was not obtained from the mother at the onset of the disease merely emphasizes the extreme importance of a careful history. It was not until this clue was uncovered that a final diagnosis was definitely established.

An unusual feature in this patient was the atypical distribution of the rash, which in the early stages of the disease was first found on the thorax and then spread to the extremities. In spotted fever the rash usually occurs first on the extremities and later spreads to the rest of the body.

Bucks County, Penn., is heavily infested with *Dermacentor variabilis* ticks. During the tick season many people in this county are bitten, but the patient reported is the first one to develop spotted fever in the northern part of the county within the last three years.

SUMMARY

Rocky Mountain spotted fever in a 4-year-old child was effectively treated with para-aminobenzoic acid. It is hoped that the drug will be used more frequently in the treatment of this dread malady, and the results promptly reported.

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POSTSCARLATINAL GANGRENE WITH PROLONGED PROTHROMBIN TIME

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DURHAM, N. C.

A RARE complication of scarlet fever is gangrene of the extremities associated with extensive hemorrhages; in 37,000 cases of scarlet fever at Municipal Contagious Disease Hospital before 1934, Dick and associates[2] observed one patient with gangrene, and found only fifteen previously reported cases. Since then Cust,[1] Hoyne and Smollar[3] (who surveyed 30,000 cases of scarlet fever) Lagréze,[4] and Stupenengo[7] have each added one case to the literature. In addition, a similar type of gangrene has been reported following chickenpox.[6, 8]

The clinical picture is that of an extensive fulminating gangrene, usually beginning from nine to twenty-three days after the onset of scarlet fever, from which an apparently uneventful recovery has been made. In at least nine of the twenty cases, the gangrene has been severe enough to require amputation of one or both lower extremities. The distribution tends to be symmetrical, most often occurring over the malleoli, knees, and iliac crests. The sharp line of demarcation of the gangrenous areas is striking. In only one case[2] has internal bleeding been noted. There is a remarkable lack of toxic signs, blood cultures when taken have been negative,[1, 2, 4] and normal blood pressure has accompanied the acute process.[1] The period of active bleeding has been limited to several days,[3] and once the bleeding has stopped there have been no exacerbations.

Hematological studies are incomplete in most of the reported cases. However, Dick's patient[2] had 150,000 platelets, bleeding time 5 minutes, and clotting time 5½ minutes; while Cust's patient[1] had 36,000 platelets, bleeding time 7 minutes, and a negative Rumpel-Leede test; and Lagréze's[4] had 164,000 platelets, bleeding time 2 minutes, and clotting time 8½ minutes with a positive Rumpel-Leede test. No prothrombin estimations are reported in the literature.

The pathologic findings are variable. Four of the fifteen cases reviewed by Dick and associates[2] showed patients with thromboses in the amputated limbs, but their own patient showed only recent thrombophlebitis without thrombi. No arterial emboli were found in the amputated limbs of Cust's patient,[1] while microscopic sections of the muscles just above the gangrene in Hoyne's patient[3] revealed acute myositis associated with panarteritis of most of the arterioles and no change in the venules.

The following is the only one out of sixty-five patients with scarlet fever at Duke Hospital to show gangrene. It is presented because of the striking abnormality of the blood clotting mechanism.

From the Department of Pediatrics, Duke University School of Medicine.

CASE REPORT

C. F., a 23-month-old white girl, was admitted to Duke Hospital Jan. 6, 1946, because of ecchymoses over the extremities of twenty-eight hours' duration.

History.—The patient has seven normal, older siblings and one brother who died in infancy of pyloric stenosis. Her mother has urticaria and a paternal aunt has asthma, but there are no blood dyscrasias or hemorrhagic diseases in the family. The child had always been a feeding problem, and refused all food except cow's milk, potatoes, cereals, and an occasional orange. She had never had any allergic or hemorrhagic manifestations, and no contagious diseases until the present illness. Tuberculin test six months before admission was negative. During the month prior to admission she had had no contact with poisons or medication of any kind except paregoric, aromatic spirits of ammonia, elixir of malto-pepsin, Upjohn's Vitakon and boric acid-glycerin ointment for the skin.

Present Illness.—Three weeks before admission the child had a febrile illness with an erythematous rash, followed by desquamation which was marked over the palms and soles. As the rash faded there was a vesicular eruption around the lips, but for one week before admission she apparently was well. Another child in the family had a similar rash ten to fourteen days before the patient. Twenty-eight hours before admission, the patient complained of pain in the right leg, and a red macule about 2 cm. in diameter was noted above the lateral malleolus of the right ankle. Within two hours, petechiae and ecchymoses covered the leg and buttock and a similar process was beginning on the other leg. Hot compresses were applied and the child was put to bed where she was playful but refused all food except milk. Eight hours before admission, a purple area started on the right shoulder and spread rapidly.

Physical Examination.—Temperature was 38.3° C. (101° F.); pulse, 130; and blood pressure, 108/68. The patient was a well-developed, well-nourished, 23-month-old female child standing in bed and using all extremities well except the right arm, on which there was an extensive, well-demarcated, purple ecchymosis extending from the shoulder to the elbow. There were scattered petechiae over the remainder of the arm and hand; the arm was moderately swollen and the hand slightly so; the radial pulse was good, although the upper arm and shoulder were cold. The skin over the knees had a bluish tinge from innumerable petechiae; small ecchymotic areas were beginning on the buttocks; petechiae were thinly scattered over the remainder of the legs, thighs, buttocks, and the right side of the trunk anteriorly; the remainder of the skin and mucous membranes were very pale without petechiae or jaundice; and the posterior tibials and dorsalis pedis pulses were strong bilaterally. The upper respiratory tract was not remarkable. Examination of the heart showed the point of maximal impulse just beyond the nipple line, regular rhythm, rapid rate, and sounds of good quality without murmurs; the lungs were clear; the spleen was barely palpable at the costal margin; the liver was not palpable; there was no abdominal tenderness; and there was no evidence of bleeding from any of the body orifices.

Course in the Hospital.—

First Hospital Day: After admission at 10:30 P.M. the ecchymotic areas continued to enlarge, but the patient did not appear toxic. Laboratory findings were: Hemoglobin, 7.0 Gm. per 100 c.c.; red blood cells, 3,310,000; hematocrit, 21.8 (cor.); white blood cells, 32,170, with 79 per cent polymorphonuclears, 11 per cent juveniles, 2 per cent myelocytes, and 8 per cent small lymphocytes. Platelet count was 100,000, and platelets appeared normal on the stained smear. Tourniquet test was negative. The red cells settled rapidly to the bottom of the Wassermann tube, and in eight hours there was no evidence of a clot in the red cell layer or the supernatant plasma. Kahn, Kline, and Mazzini tests were negative, and blood cultures were sterile. Stool showed no gross or microscopic blood.

Second Hospital Day: At about 2:00 A.M., the patient was standing in her bed crying for water when she vomited clear watery material and suddenly became semicomatose, though her blood pressure remained 108/68. Transfusions were started immediately, and she received 500 c.c. of bank blood within the next twenty-four hours as well as penicillin and Vitamin

K, and the extremities were loosely wrapped in sterile cotton. Despite this the ecchymoses continued to enlarge and by afternoon she appeared as in Fig. 1, *A*. Clotting time by Lee-White's macro method showed the blood to remain fluid after forty-eight hours, except for a tiny clot that appeared in about two hours. By the capillary tube method the clotting time was 16 minutes; the bleeding time (Duke's method) was 8 minutes. The prothrombin

Fig. 1.—*A*, appearance of the child on the second hospital day. *B*, appearance of the child after the cessation of bleeding (fourth hospital day). *C*, the disarticulated right arm. The slough of the upper arm included only skin and subcutaneous fat.

times (Quick's simple clinical method) were 8 minutes, 56 seconds, checked at 9 minutes, 10 seconds (control, 17 seconds), and 8 minutes, 8 seconds (control, 21 seconds). Tourniquet test (Rumpel-Leede) was again negative. Platelets at this time, however, were less than 1,000 per cubic millimeter* and were very rare on the stained blood film.

*Platelet counts were done on a fresh supravital preparation by comparing the number of platelets to the number of red blood cells.

Third Hospital Day: In the morning the areas of gangrene were still spreading, and a pinkish halo was appearing around the margins (Fig. 1, *B*). The right radial pulse was no longer palpable though the dorsalis pedis pulses were good bilaterally. The spleen was now palpable about 2 cm. below the costal margin as was the liver, and the child had a slight nosebleed. The hemoglobin had dropped to 4.5 Gm., platelets were 25,000, and white blood cells were 58,400. For the only time throughout her course there was microscopic blood in the stool though none in the urine. About noon the child suddenly became cold, clammy, and unresponsive. Banked blood was given immediately by the pressure method followed by a continuous intravenous infusion of saline, dextrose with accessory vitamins, and freshly drawn, citrated blood. By 2:00 P.M. the ecchymotic areas had stopped spreading, and the child's color became good (Fig. 1, *B*).

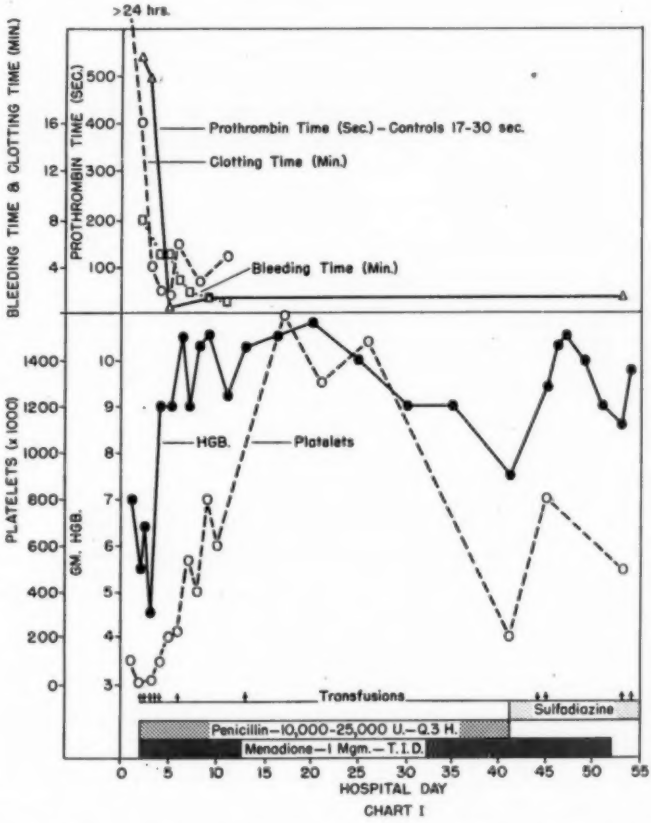

CHART I

Subsequent Course: By the fifth hospital day the blood findings approached normal: Hemoglobin, 9 Gm.; red blood cells, 3,000,000; platelets, 200,000 with a prothrombin time of 15 seconds (control, 22 seconds), bleeding time, 5 minutes, and clotting time, 2½ minutes (capillary method). From this time on, the blood findings were not remarkable except for a platelet rise to 1,600,000 on the seventeenth hospital day (Charts I and II). On the eighteenth hospital day the fibrinogen was 0.57 Gm. and later fell to 0.43 Gm. per 100 c.c. plasma.

After the bleeding stopped, the hemorrhagic areas rapidly became definitely gangrenous. The limbs were kept in loose bandages of sterile cotton as long as the tissues appeared

viable, but on the eleventh hospital day dry rayon dressings covered with pressure bandages were begun. On the fifteenth day the arm spontaneously disarticulated at the elbow, slough developed over the buttocks and knees, and self-amputation of the toes began. The course was complicated by a mild pyelitis, a pyocyaneus infection of the denuded areas, and a stubborn miliaria-like rash of the skin which made grafting impossible. The patient was discharged against advice seven months after admission. At this time the humeral stump as well as the other areas had granulated well but still had not epithelialized completely, and there was some contracture of both knee joints. Local treatment consisted of débridement, saline baths, pressure bandages, and physiotherapy. The temperature curve (Chart II) was of a septic type with short periods of almost normal temperature during the last four months of her hospital stay. There was no further bleeding tendency.

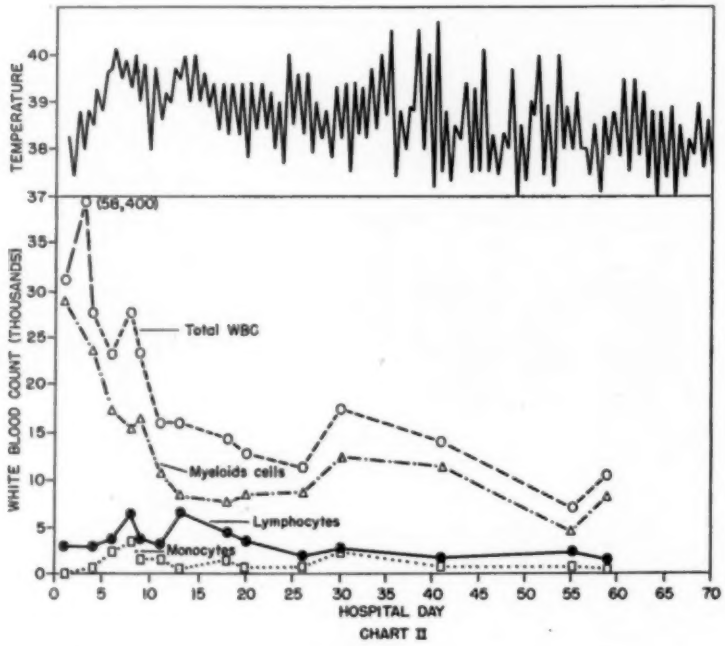

CHART II

DISCUSSION

In the previously reported cases the emphasis has been on the gangrene[1-3] and the blood picture has not been extensively studied; however, in our case we had the opportunity of watching the gangrene develop and of following the blood picture during the development and recession of the gangrenous process. When the patient was first seen, the picture was that of a fulminating purpura, yet the platelets were 100,000, and appeared adequate on the stained smear. Clinically, then, the period of most active bleeding preceded the platelet fall; furthermore, the tourniquet test was negative. The most unusual feature of this case was the prolonged prothrombin time done by Quick's bedside method[5] in which care was taken to add the full amount of thromboplastin. It is not known whether the prolongation of the clotting in this test is due to

deficiency in prothrombin alone or whether an excess of heparin or diminished fibrinogen played a role. It was impossible to secure sufficient blood for testing these at the time of active bleeding.

The very high leucocyte count which reached its maximum at the height of the bleeding is also interesting, as is the actual and relative increase in mononuclear cells and platelets with high fibrinogen during the active period of slough (Chart II). The disarticulated arm (Fig. 1, *C*) showed only necrotic tissue.

SUMMARY

1. A review of the literature of postscarlatinal gangrene reveals twenty cases.

2. A new case of postscarlatinal gangrene with thrombocytopenia and prolonged prothrombin time is presented with the laboratory findings.

The authors wish to thank Dr. Jerome S. Harris for his helpful suggestions in the preparation of this article for publication.

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EXPERIENCES WITH JAPANESE PEDIATRICS

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PHILADELPHIA, PA.

IT IS now generally recognized that the American occupation of Japan is proceeding with remarkable smoothness. On all sides American troops are mingling freely with the Japanese population. It is not the purpose of this account to discuss at length Japanese psychology or to attempt to speculate on the proportions of purely external politeness and of heartfelt friendliness which are making up the warm reception being accorded the occupation forces. As a member of the Army Medical Corps, I was able to utilize a recent five- and one-half-month stay to advantage by studying Japanese medicine and pediatrics. Returning well stocked with reprints and personal communications, I feel that the facts to be presented are reasonably accurate.

At this point, a brief description of the development of Japanese medicine seems in order. Japanese medicine became oriented along western lines after the opening of the country to outside influences about a century ago through the efforts of Commodore Perry. Actually, it was well toward the end of the nineteenth century before much progress was made. This coincided with the Golden Era of German medicine. For this reason, Japan came overwhelmingly under the influence of the leaders of medicine in Germany and Austria. With some exceptions, this condition held until the present war. As a result, German texts and publications were widely read, and large numbers of promising workers were sent to the clinics of Germany and Austria. On returning to their homeland, these men labored to set up replicas of the establishments where they had studied, and German became the scientific language of the medical profession. Up until the present time, clinical records, writings, and dissertations are literally seeded with German terms and phrases; this applies to diagnostic terms in particular.

Following German lines, faculties were set up, with "professors" ruling the clinics in rather autocratic fashion. A sharp cleavage between the full-time teacher and the practicing physician was established. The latter have had virtually no access to public or teaching hospitals. This appears to have brought about an ultrascientific, impersonal attitude on the part of the teacher, while the practitioner, on the other hand, frequently sets up a small private hospital, usually poorly equipped, and regards medicine largely from a commercial standpoint. The oriental tendency to contemplate suffering with more indifference than we do, the great density of population, and the caste system (the physician and especially the "professor" naturally falling into an upper bracket) serve to accentuate the situation.

During the war, the Government made terrific demands on the medical profession. The "home front" was greatly depleted, supplies were scarce, and

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buildings were allowed to deteriorate unbelievably. It would almost seem as though the Japanese have better luck in maintaining their flimsy, native structures than the Western style buildings. It was interesting to hear that few of the senior members of the medical faculties were called to military service. A personal opinion expressed by one eminent teacher was that "perhaps the military surgeons feared the competition of men from teaching centers."

Medical education in Japan has lacked uniformity. The standards of the medical faculties of the seven Imperial Universities (nine in pre-V-J days) are the highest. In addition, there are about seven government schools of university rank. These also have fairly high standards. Three private medical schools, all situated in Tokyo, are of university rank and have good reputations.

In Japan there are also medical professional schools of lower rank. In prewar days, there were six of these for men and three for women. Women cannot attend the other institutions except for work on a graduate level. During the war, countless emergency courses and further medical professional schools were opened. As a result, one would assume the presence of a large number of poorly trained graduates. The good schools require a premedical course, extending about the same number of years as our own. The medical professional schools have combined premedical and medical courses lasting between four and five years in ordinary times.

Internships as we know them are not generally available. A clerkship is served during the medical course. Further practical experience in clinics is gained by assistantships which are always along specialized lines. Medicine is a very popular profession and the students are selected from a large field of applicants on a competitive basis. "Weeding-out" examinations are given on several occasions. The tuition, especially in the government schools, is relatively low.

Along the lines of modern equipment Japanese medicine is far inferior to our own. Much of the apparatus is old. Central supply rooms are not generally known. At medical centers each specialty usually maintains its own buildings and tends to function independently of the others. The resources of Japan are meager. Furthermore, most of the substance of the country has been depleted by war for some years. At the present time, all medical leaders are keenly aware of the strides made by American medicine and also of their own backwardness. They are anxious to acquire knowledge coming from our shores.

With this background, the reader will, perhaps, understand better the personal pediatric experiences to follow.

Being stationed near the Kyushu Imperial University, I had excellent opportunity to become acquainted with Japanese pediatrics. This school was regarded as having one of the best faculties in the country. The medical school and hospital was a large plant consisting of about twenty buildings. The total bed capacity was said to be about 1,000. Externally, some of the buildings were quite modern and even impressive. However, most of them were in need of considerable repair. The prewar enrollment was about 565 students in the medical course.

The pediatric clinic was housed in an old, two-story structure of frame and plaster with a bed capacity of sixty. A laboratory, formula room, classroom, library, and faculty office comprised the remainder of the structure. Private rooms were available. In Japan, members of the family always stay with the patient; they frequently cook for him and even nurse him. This complicates the picture, especially in the wards.

The library was fairly complete and up to date until the time of Pearl Harbor, and leading pediatric journals of American and German origin were available.

The staff consisted of a professor and an assistant professor. There were a number of instructors and about twenty assistants. These served for an average of three years, thus obtaining pediatric training.

My first visit to the Children's Clinic was unexpected and unannounced. However, I was immediately ushered into the presence of Professor Munenori Enjoji, the head of the pediatric department. I was received with all the usual politeness of the Japanese. After some minutes of conversation in English which progressed fairly well, we discovered that German was an even better tongue in which to converse. It was soon brought out that his training had been in the United States, Germany, and Austria. Upon returning to Japan in the early days of the war, he became the third incumbent of the Chair of Pediatrics of the Kyushu Imperial University, which position he still holds.

Professor Enjoji and I became well acquainted and met weekly for the discussion of pediatric problems and the interchange of ideas. From him I obtained a brief history of Japanese pediatrics.

In 1888, Hirota, a pupil of Kohts, then Professor of Pediatrics at Strassbourg, became director of the Children's Clinic at the Imperial University in Tokyo. In 1895, Ito, a student of Heubner in Berlin, became head of the Children's Clinic at the prefectural hospital in Fukuoka. From this developed the Kyushu Imperial University. In 1903, Hirai, who had studied under Czerny in Breslau, became the head of the pediatric department at the Imperial University in Kyoto. These men then became the early leaders of Japanese pediatrics.

At the Kyushu Imperial University, Ito was succeeded by Mita, who in recent years became emeritus professor, to be succeeded by Enjoji. It is interesting to note that the history of Japanese pediatrics is not much shorter than that of pediatrics in this country.

In prewar days, there were 3,000 pediatricians in Japan, out of a total of 65,000 licensed physicians. It is not possible to state whether these were exclusive specialists, since there are no specialty boards in Japan. Pediatricians are usually located in the larger centers.

Professor Enjoji and his co-workers read avidly any journals I was able to lend them. Recent American pediatric texts were literally devoured. Enjoji impressed me as alert and well trained. His clinic, while old and in poor repair, was clean and orderly. He appeared to be deeply interested in pediatrics and was well aware of the shortcomings of Japanese pediatrics. He repeatedly

stressed to me the need for much more emphasis on preventive pediatrics and on growth supervision than was being made in Japan.

Generally, the pediatric facilities are represented by the children's clinics of the various medical faculties, children's departments in prefectural hospitals, and by the work of the private pediatricians. The last group frequently maintain their own small private hospitals. Red Cross hospitals and hospitals supported by various Christian missionary groups are usually of a model type in respect to the buildings, their maintenance, and the medical care given. St. Luke's Hospital in Tokyo, the International Red Cross Hospital in Kyoto, and the Hospital of Our Lady in Tokyo are notable examples.

On the other hand, the communicable disease hospitals do not appear to be well run. They have the atmosphere of a "pest-house," offering for the most part, only a segregated environment, and providing little active treatment.

It must be emphasized that systematic pediatric supervision and the use of routine immunization are very rare practices in Japan. The exception to the latter would be smallpox vaccination which is done fairly universally since it has been decreed compulsory, the regulations requiring one vaccination within six months after birth and another in the tenth year of life. However, occasional lapses occur, and smallpox is not unknown in Japan. In fact, during the past year there has been a considerable number of outbreaks which no doubt, are related in part to the general disintegration of the war and its consequences. Some diphtheria immunization is done, as there is considerable diphtheria in Japan.

The teaching of pediatrics is carried out with much emphasis on didactic methods. In proportion to the large student bodies the number of both inpatients and outpatients available for teaching is not very large. At present, much thought is being given to the revision of the curriculum along American lines. There is much discussion given to the introduction of democratic methods in the conduct of the entire medical faculty setup. I was frequently asked how professors were appointed in the United States and especially how they were disposed of if unpopular or unsatisfactory.

There appeared to be an abundance of assistants at the various children's clinics. These are the equivalent of our pediatric residents and fellows. They seemed very eager to learn in the usual fashion of the Japanese, with notebooks, pencils, and pens always in evidence.

Judged by our standards, most of the equipment is quite meager in the average children's clinic. This is especially true in regard to facilities for parenteral therapy. Rubber is very scarce, hence much of the tubing is in poor condition. Blood transfusions are usually given with 50 c.c. or 100 c.c. syringes; the total quantity is small according to our standards. In general, one can safely say that equipment is twenty to thirty years behind our own.

Therapy is conducted along lines similar to ours. Penicillin is now becoming available; sulfapyridine and sulfaguanidine are the chief sulfonamides; sulfathiazole and sulfadiazine are little known. Biologicals are quite scarce. Diphtheria antitoxin is available, but only in small quantities. One cannot escape the impression that while therapy is important, immediate results are not

as paramount as with us. In the university clinic the patient is distinctly subservient to the physician. One sees many patented, "coal tar" products in pharmacies. Again this seems to indicate the German influence.

Medical libraries appear to play an important part in medical education. However, since Pearl Harbor they have stagnated. Textbooks are almost impossible to obtain and most students must study from notes.

Research seems to be stressed a good bit. In fact, one receives the impression at times that it is forced like a hothouse plant. At the present time the work in pediatrics is largely clinical research. Formerly, much attention was given at the Kyushu Children's Clinic to the bacteriology of the dysenteries.

From an economic standpoint, the medical teacher is poorly paid at present. His salary is fixed and has not kept pace with the inflationary price rise. He has no opportunity for adding to his income from private practice or even consulting work. He seldom owns an automobile. Nevertheless, his prestige is still great.

The physician in private practice has somewhat better opportunities for making a living. Compulsory health insurance exists for certain classes of workers, and there are many voluntary health insurance societies. However, fundamentally, private practice is conducted independently by the physician. As previously stated, many operate small hospitals of their own, but these, as a rule, are poorly equipped. One of the leading pediatricians in Fukuoka goes about on a bicycle. House calls are less frequently made than in the United States. Since telephones are scarce, this instrument plays a less important part than it does in American medicine.

SPECIFIC PEDIATRIC PROBLEMS

The high birth rate of the Japanese is well known. Most families have at least six children; in fact, to have less is almost not respectable. While some of this is due to the expansionistic policy, one does gain the impression that children are genuinely liked for their own sakes. Boys are more welcome than girls. Giving birth and rearing children are regarded as natural functions. A midwife usually attends the delivery, which characteristically takes place at home; hospitals and obstetricians are largely reserved for pathologic cases and wealthy persons.

Growth and Development.—The average birth weight of a full-term, male infant is approximately 6 pounds, 11 ounces (3.06 kg.), and of a full-term, female infant, 6 pounds, 8 ounces (2.95 kg.). This is, of course, less than the figure for the United States. The length is 49.4 cm. for boys and 48.5 cm. for girls, which is lower than the American figures of 50.4 cm. and 49.7 cm., respectively.

At 16, the Japanese boy's height averages 147.7 cm. and the girl's, 144.1 cm., in contrast to the figures of 171 and 167 cm. for American boys and girls, respectively.

The weight of boys at 6 years is 17 kg., at 12 years, 30 kg., and at 16 years, 40 kg. American weights average 20.4, 39, and 61 kg., respectively, for the same age groups.

Japanese girls weigh an average of 16.5 kg. at 6 years, 30 kg. at 12 years and 40.4 kg. at 16 years. Average American weights are 19, 39, and 56 kg. for the same age groups.

From tables made available to me I would conclude that motor development and mental development in Japanese children are comparable with our own children.

Problems of Infancy.—Breast feeding is taken for granted in Japan. In fact, the big problem is to educate mothers to discontinue nursing their infants at a reasonable time. "Late weaning disease" is an entity under much discussion. In previous times beri-beri was a problem of greater extent than recently.

Anemia, poor muscle tone, and rachitic changes are all described as the fate of a late-weaned infant. Many children are not weaned until well into the second year. During this period of protracted nursing virtually no other nourishment is given. It would appear that this factor is responsible for the above manifestations.

Under the influence of pediatric clinics some progress is being made toward weaning at one year. When a breast milk substitute is needed, quite a problem is faced. Animal milk is very scarce. Cow's milk can be obtained in small quantities. Thin rice gruel is the usual substitute for milk; obviously, it is far from satisfactory. Soybean milk has become quite popular and the results with its use are quite good. A synthetic "milk" made up from peptonized sardines, millet jelly, cod liver oil, sesame oil, and garden radishes has been used to some extent, and the results were fairly satisfactory.

Dysentery and Dysentery-like Diseases.—These have always offered a considerable problem in Japan. The universal use of "night-soil" for fertilizer, the abundance of flies, the predominant use of "privies" rather than flush toilets, all contribute to this group of diseases. A good deal has been done on the bacteriology of these cases by the Japanese. Mita, the Emeritus Professor of Pediatrics, is credited with considerable work, especially with isolating a group of paradysentery organisms.

Therapeutically, sulfaguanidine or sulfapyridine, diet, and fluid balance comprise the therapy. It is claimed that sulfapyridine is more effective than sulfaguanidine. Rice gruel is used largely as the first form of nourishment in these cases.

During the past twenty-eight years, Mita has studied 2,676 patients with dysentery. Of this group, causative organisms in 1,750 patients were isolated.

An interesting entity described in Japan is "ekiri." This is seen not only in cases of acute colitis, but also in some cases of high fever in association with many infections. Symptoms are sudden onset, vomiting, stupor, delirium, convulsions, and coma. The susceptible age is generally from 2 to 6 years. While many theories have been advanced in regard to etiology, an abnormal stimulation (spasm) of blood vessels and of the autonomic nervous system as a whole, coupled perhaps with an "ekiri diathesis" is set up as an explanation.

The etiology and nature of "ekiri" appear somewhat obscure. One wonders whether it merely represents a terminal picture of an overwhelming infection. The Japanese, endorsing the idea of spasm, have employed atropine and claim some successful results. A sharp reduction in mortality has been reported.

Tuberculosis.—Tuberculosis is without doubt the biggest public health problem in Japan. Tuberculous meningitis is a very frequent form in infancy and early childhood. In 393 patients studied, 17.74 per cent were in infancy and 64.5 per cent in early childhood.

The mortality from all forms of tuberculosis in children under one year of age was 75 per cent, from 2 to 5 years inclusive it was 38 per cent, and from 6 to 11 years inclusive, 14.4 per cent. During puberty the death rate increased to 28.26 per cent.

The percentage of positive tuberculin reactions among school children in Fukuoka ran as follows:

First Grade—12.8 per cent positive reaction
Second Grade—17.5 per cent positive reaction
Third Grade—21.7 per cent positive reaction
Fourth Grade—25.5 per cent positive reaction
Fifth Grade—27.4 per cent positive reaction
Sixth Grade—31.2 per cent positive reaction

Tuberculosis is the leading cause of death in Japan. In 1938 the death rate for the entire population was 206 per 100,000. As a comparison, during the same year in the United States registration area, the death rate was 49 per 100,000.

Atomic Bomb Disease.—A small group of children (twenty) exposed at Hiroshima and Nagasaki were studied and reported. These were children who had survived the initial damage. Symptoms consisted of depilation, diarrhea, hemorrhage into the skin, sore throat, gingival hemorrhage, and ulceration of the mouth. All of this group had some leucopenia and anemia. Bone marrow studies revealed an increase in the young forms of granulocytes (40 to 60 per cent). It was concluded that children subjected to heavy irradiation died shortly after the bombing. The children who survived appeared to recover more satisfactorily than corresponding cases among adults. It was felt that blood regeneration was more active in children. Four of the twenty died. Diarrhea was marked in one patient, petechial hemorrhages in another. Ulceration of the oral cavity and convulsions were the most striking symptoms in two.

Intestinal Parasites.—Due to the widespread habit of fertilizing with "night-soil," parasitic infections are quite abundant. Flush toilets are quite rare, except in modern buildings. A survey of 581,809 persons in 1937 revealed 48 per cent carrying parasite eggs. *Ascaris lumbricoides* accounted for the largest number, being found in 83 per cent. Hookworm was found in 22 per cent. Multiple infections are frequent. *Diphyllobothrium latum, Trichuris trichiurd,* and *Enterobius vermicularis* are frequently seen. Liver flukes (*Clonorchis sinensis*), intestinal flukes (*Metagonimus yokogawai*), and lung

flukes (*Paragonimus westermani*) are occasionally encountered. Several localized endemic areas of *Schistosomiasis japanica* are found in certain parts of Japan. For the most part, the intestinal parasitic infections seen most commonly do not seem to affect the welfare of the children to any appreciable degree.

Chronic Lead Poisoning.—In 1892, Professor Hirota first described a so-called meningitis in infants. The cause remained obscure until 1924, when Professor Hirai discovered that it was a form of lead poisoning. A lead-containing face powder used by the nursing mother was the cause. This correlated with the age of greatest incidence, namely, 6 to 12 months. Basophilic granulation of the erythrocytes and the lead gum line led to the diagnosis. Following demonstration of the etiology the Japanese Government passed a law forbidding the inclusion of lead in face powder.

Poliomyelitis.—Cases have been seen, but they are sporadic rather than epidemic in form. From 1931 to 1940 the children's clinic at the Imperial University in Tokyo treated 685 patients. One hundred fifteen were under 1 year of age, 264 from 1 to 2 years, and 169 from 2 to 3 years. June, July, and August saw the largest number of patients. All of these patients had the paralytic type. A series of forty-nine patients with abortive poliomyelitis is also described.

Japanese Type B Encephalitis.—While this disease appears to have occurred as far back as 1871, it was first established as a characteristic entity in 1924. The mortality rate is as high as 60 per cent, mostly in older patients. The onset is abrupt, with high fever, headache, beclouded consciousness, and various degrees of paralysis. Complications such as pneumonia or urinary tract infections account for many of the deaths. The spinal fluid is clear but under pressure. The cell count is 25 to 500. At first, 50 per cent of the cells are polymorphonuclears; later, lymphocytes predominate. There is an increase in the total protein and globulin. Definite diagnosis can be established by demonstration of neutralizing antibodies and complement fixation reaction. Mouse inoculation is also employed.

In 1937, Segawa tested the neutralizing potentialities of blood sera of the inhabitants of Tokyo, dividing them into age groups. In newborns he found 78 per cent of sera contained neutralizing antibodies. In the age group of 1 to 3 years no neutralizing capacity was demonstrated. With increasing age the percentage again increased so that in the group from 40 to 60 years, 66 per cent of all sera sampled contained neutralizing antibodies.

Miscellaneous Infections.—Rat bite fever, leptospirosis, tsutsugamushi fever are encountered. Typhoid and paratyphoid fever occur at times. Leprosy is seen, and venereal diseases are common.

Nutrition.—It was not possible to obtain any definite information concerning the incidence of malnutrition and vitamin deficiencies among the children of Japan. Needless to say, many of them are subsisting on a diet both deficient in quantity and quality. Fukuoka, being a relatively small city in a fairly rich agricultural area, does not suffer acutely from the food shortage as do the large industrial cities of the main island of Honshu.

Superficial observations indicate that many children are underweight. The stunting effect of the diet seems to have been fairly well established. Reports of children being too weak to go to school were obtained. A longer period of study will be required to determine fully the results of the food shortage.

CONCLUSION

It is felt that a better understanding of the medical situation in Japan will ultimately improve the outlook for world peace. At no time in the history of that country have its people been more anxious to learn American methods. In medicine this is especially the case. A vacuum has been created with the collapse of German medicine, and we can determine to a great extent what will fill that space.

If American medicine can be brought to the Japanese in all of its fullness, so that they will assimilate not only the cold facts but also some of the higher spiritual aspects, then world peace will have been furthered. In this spirit the present account is offered.

Case Reports

NEPHROSIS

A Case Treated With Concentrated, Low Salt, Human Serum Albumin

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REFERENCES to the treatment of nephrosis with concentrated, low salt, human serum albumin have recently appeared in the literature.[1, 2, 3] We present this case as we believe it is the first so treated to be reported in the American pediatric literature.

F. M., a white male, aged 4 years, 4 months, was admitted to the New York Post-graduate Medical School and Hospital on Sept. 17, 1945, with a chief complaint of coryza of seven days' duration and edema of six days' duration. The boy had been in excellent health all his life until one week before admission. At that time, he developed a "running nose" and "slight cough" without fever. The following day his eyes and ankles were slightly swollen. The third day of illness, his abdomen and legs began to swell. The family history and past history were noncontributory.

The child's admission temperature was 99.4° F., his pulse was 82, respirations were 24, and blood pressure was 122/80. He was well developed and moderately well nourished, with generalized pitting edema and moderate dyspnea. The eyelids were moderately edematous. There was a mild pharyngitis with a postnasal drip. The heart was clinically negative, but there were medium, moist râles at both lung bases. The child's abdomen protruded moderately; there was a shifting dullness. Both lower extremities showed a 4 plus, pitting edema as high as the knees. The child weighed 49 pounds on admission; his weight before this sudden illness had been 36 pounds.

Admission blood count was within normal limits; the urine revealed 3 to 5 white blood cells per high power field, no red cells, an occasional hyalin and coarsely granular cast, and 2 plus protein. The nonprotein nitrogen was 60 mg. per cent and calcium was 8.3 mg. per cent. Serum protein values are given in Fig. 1 for comparison with later findings. Blood cholesterol varied between 500 and 600 mg. per cent.

The child was placed on a high protein diet (3 Gm. per kilogram of body weight per day) which was salt free. Fluid intake was 500 or 600 c.c. a day; output could not be measured because of incontinence.

Blood pressure findings repeatedly varied between 90/70 and 120/88. Urinalysis remained the same; at no time were more than 6 or 8 red blood cells present per high power field, and most of the time none were seen. An Addis count done one week after admission showed a marked increase in the number of casts, normal red, white, and epithelial cells. The nonprotein nitrogen remained normal.

Intensive therapy with ammonium chloride and magnesium sulfate failed to cause diuresis; the patient remained very edematous and weighed about 48

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pounds. Over a period of weeks 250 c.c. of blood plasma daily were also given, with no improvement. Whole blood transfusions were given as needed to maintain the red blood count and hemoglobin at high levels. The ascites increased to an extreme degree, so a peritoneal tap was done Nov. 28, 1945. The fluid lost by this procedure was rapidly replaced and the child was soon as edematous as before.

In the early part of January, 1946, adequate doses of thyroxin, ammonium chloride, and mercupurin were administered without effect. Urine showed 3 plus protein.

Early in February, a careful check was made on the food and salt intake. Although the child was offered a diet containing 3 Gm. per kilogram of body weight in twenty-four hours, because of his poor appetite, we was taking only .5 Gm. per kilogram. Although his diet was the accepted salt-free hospital diet (Table I), his daily salt intake was actually 1 to 2 Gm. a day. In addition,

TABLE I. SALT FREE, HIGH PROTEIN DIET WITH AND WITHOUT DIALYZED MILK AND AMIGEN

	WITH UNDIALYZED MILK AND NO AMIGEN				WITH DIALYZED MILK AND AMIGEN			
MEALS	FOODS* (Salt free)	AMOUNTS	GM. PROTEIN	NaCl	FOODS† (Salt free)	AMOUNTS	GM. PROTEIN	NaCl
Breakfast	fruit juice	½ cup	1	.008	fruit juice	½ cup	1	.008
	cereal (Cream of Wheat)	¼ cup	0.5	.012	cereal (puffed rice)	¼ cup	0.5	.013
					bread	1 slice	3	.023
	bread	1 slice	3	.023	butter	1 tsp.		.001
	butter	2 tsp.		.002	milk }	1 cup	6	.068
	milk	½ cup	3	.260	amigen }	2 tsp.	4	
					10 A.M.			
					orange juice		1	.008
					with 1 egg		3	.027
					yolk and 2 tsp. amigen		4	
Noon meal	meat				meat (beef)	1 oz.	6	.051
	cheese				cheese			
	eggs				eggs			
	potato				potato	½ sm. one	1	.030
	vegetable				carrots	¼ cup	0.5	.013
	bread	1 slice	3	.023	bread	2 slices	6	.048
	butter	1 tsp.		.001	butter	2 tsp.		.002
	fruit				fruit			
	milk	1 cup	6	.520	milk			
	ice cream	½ cup	10	.233	ice cream }	½ cup	10	.034
					amigen }	2 tsp.	4	
Night meal	meat				meat (chicken)	1 oz.	6	.048
	cheese				cheese			
	eggs				eggs			
	potato				potato	½ sm. one	1	.030
	vegetable				vegetable			
	bread	1 slice	3	.023	bread	1 slice	3	.023
	butter	1 tsp.		.001	butter	1 tsp.		.001
	fruit (canned pears)	½ pear	0.5	.010	fruit (apple sauce)	¼ cup	0.5	.004
	milk	½ cup	3	.260	milk }	½ cup	3	.034
					amigen }	1 tsp.	2	
Bedtime	milk	½ cup	3	.260	milk	½ cup	3	.034
Totals for day			36	1.636			68.5	.500

*Food habits: Child refused meat, vegetables, and potato at both meals, which, if eaten, would have increased the protein intake and also raised the NaCl still higher.

†Refused vegetable at night meal.

he was receiving salt in the plasma and blood. Each 250 c.c. of plasma contains 1.05 Gm. of salt; each 250 c.c. of whole blood contains 0.58 Gm. of salt. He had not been given intravenous Amigen because each 1,000 c.c. of amigen contains 2.0 Gm. salt. Therefore, his daily salt intake was 2 to 3 Gm. The child was taken off all plasma and put on 50 Gm. of amigen daily by mouth. This was done by adding powdered amigen to grape juice flavored with lemon juice and sugar, and to orange juice. Amigen was also added to ice cream, jello, and custards. Despite this added protein offered, the child's total proteins could be raised to only 1 Gm. per kilogram of body weight in twenty-four hours, since he often refused the food that contained the amigen. Therefore, he was given 50 Gm. of amigen in fruit juice every evening by gavage. This was given in the

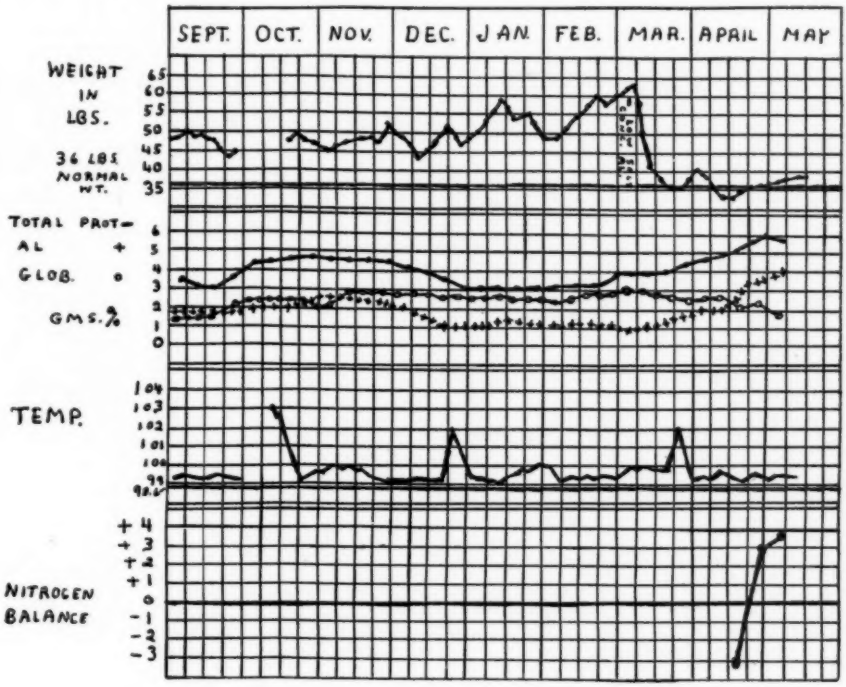

Fig. 1.

evening in order to prevent anorexia as much as possible. Even by this method, the total proteins were only 1.5 Gm. per kilogram of body weight. During this period the salt intake was 1 Gm. in twenty-four hours. This was lowered to approximately .5 Gm. per twenty-four hours by dialyzing the milk and by using fresh vegetable juices instead of canned vegetable juices. In addition, special attention was given to the removal of salt from all foods as far as possible, and special bread was prepared. Each 100 Gm. of canned vegetable juice contains from .060 to .080 Gm. salt. Each quart of undialyzed milk contains 1.72 Gm. salt, but by dialyzing the milk in the hospital, this value was brought down to .340 Gm. salt per quart of milk. A commercial preparation of dialyzed milk which contains .130 Gm. of salt per quart of milk may be used; it was used on this child during the last five days of his hospital stay (Table I).

The boy continued to be edematous and ascites was very marked. His protein intake was 16 Gm. daily, or about 1 Gm. per kilogram of body weight. The urine showed 4 plus protein, and 8 to 10 hyalin casts. The albumin-globulin ratio was inverted (Fig 1).

On March 8, 1946, the child was given his first dose of 15 Gm. of concentrated, low salt, human serum albumin by slow, intravenous drip. The albumin comes in 5 Gm. quantities in vials of 20 c.c., each of which has the osmotic equivalent of approximately 100 c.c. of citrated plasma. When injected intravenously, it draws approximately 70 c.c. of additional fluid into the circulation within 15 minutes, except in the presence of dehydration. The extra fluid reduces hemoconcentration and blood viscosity. One vial contains only 0.06 Gm. of sodium. Each vial of albumin was mixed with 30 c.c. of 10 per cent glucose to facilitate intravenous injection, since the albumin alone is very viscous. Therefore, three vials were dissolved in 90 c.c. of 10 per cent glucose. It is advisable to give the albumin solution at a rate not exceeding 15 drops per minute. There was no unfavorable reaction to the albumin.

This solution was given daily for two months. After three doses the child lost 9 pounds, the edema of the eyelids completely disappeared, the edema of the ankles diminished by 50 per cent and the ascites diminished greatly. The child's appetite improved remarkably. His protein intake went up from about 1.5 Gm. to 7 Gm. per kilogram of body weight in twenty-four hours. He lost all of his edema and his weight went down more slowly after the initial loss of 9 pounds in three days, but continued to go down consistently from 50 pounds to 34 pounds within two and one-half weeks (Fig. 1). At that time, he still had a mild amount of ascites. His weight then started to increase gradually. As proof that the child was having a true weight gain, a nitrogen balance test was performed. On April 18, 1946, during a twenty-four hour period, the total nitrogen intake was 9.5; nitrogen output was 12.6 Gm. The child was, therefore, in a negative nitrogen balance of minus 3. Pyridoxin was then given in a dosage of 50 mg. daily in an effort to promote better utilization of amino acids, especially tryptophan, and thus obtain a positive nitrogen balance. A nitrogen balance test done on April 30, 1946, showed that in a twenty-four hour period the child took in 11.4 Gm. of nitrogen and put out 8.4 Gm., and was in positive nitrogen balance of plus 3. The nitrogen intake was recorded daily and was found to be between 10 and 14 Gm.

During the two-month period that the child received the concentrated, low salt, human serum albumin, the urinary protein decreased to a value of 1 plus; very few white blood cells and no casts were found. Serum proteins were altered, serum albumin increased, and globulin decreased proportionately until a normal albumin-globulin ratio was obtained (Fig. 1). Blood cholesterol fell from 850 to 300 mg. per cent.

Since the child continued to improve, the low salt, human serum albumin was discontinued on May 3, 1946. He was kept in the hospital for eleven days following discontinuation of the drug, but when blood and urinary findings were not adversely effected, he was discharged on May 14, 1946. He received the high protein, salt free diet at home.

Follow-up examinations on June 12, and July 15, 1946, were made. The child weighed 40 pounds, temperature was normal, there was no edema or ascites, and the rest of the physical examination was normal. Urine tests revealed 1 plus protein, with no other abnormal findings; blood count was normal; total protein was 5.7 per cent; albumin, 3.5 per cent; globulin, 2.2 per cent; albumin-globulin ratio, 1.6:1; and cholesterol was 220 mg. per cent. The child leads the life of a normal, active, 5-year-old boy.

COMMENT

This patient did not respond over a period of eight months to any of the accepted methods of treatment. His improvement was prompt and striking following the administration of concentrated, low salt, human serum albumin. In addition, he was on an especially rigid, salt free, high protein diet with dialyzed milk. He also received pyridoxin. Following the administration of pyridoxin, the patient went from negative nitrogen balance to positive nitrogen balance. We, therefore, believe that a rigid, salt free, high protein diet with dialyzed milk, and pyridoxine are valuable aids in the treatment of nephrosis. Naturally, further clinical studies are needed for a true evaluation.

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ADDENDUM

Since this article was submitted for publication, four additional patients with lipoid nephrosis have been treated by one of us (A. G. DeS.) in the New York Postgraduate Hospital. The method of treatment has been the same as described herein. The patient whose case record was discussed in this article was last examined on Nov. 20, 1946. He is in excellent condition.

The second child so treated has also been discharged from the hospital. He is in good condition, free of any signs of edema, and in positive nitrogen balance.

The other three children are still in the hospital. They have been under treatment for periods of two weeks to seven weeks. All three are practically free of edema and show marked clinical improvement. Two of these patients had several peritoneal taps done in other hospitals to relieve marked abdominal ascites. It is interesting to note that none of our children treated with concentrated, low salt, human serum albumin required peritoneal taps after this treatment was started.

It is our impression that the results obtained in the treatment of lipoid nephrosis with the above outlined management are far better than with any other methods we have used heretofore.

A more detailed report of this clinical experiment with control studies will be published later.

SYRINGOMYELIA, MORVAN'S SYNDROME

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IN 1883 a report by Augustin Morvan[1] in the *Gazette hebdomadaire de medecine et de chirurgie* presented seven case studies which were considered to be examples of a new disease. Characteristics of the entity were loss of pain and temperature sensations of the extremities, amyotrophy, paresis, trophic disturbances of the phalangeal bones and joints and the skin overlying these areas, and mutilation of the fingers and toes resulting principally from painless, unnoticed trauma and infections. The etiology of this syndrome was not known to Morvan, but he expressed the belief that the source of the disturbance was to be found in the spinal cord. Charcot,[2] Joffroy and Achard,[3] and later, Kalindero and Martinesco,[4] presented evidence which led them to classify Morvan's syndrome as a chronic form of syringomelia, characterized mainly by trophic changes of bones, joints, and skin. To the present time, there have been no new concepts offered regarding the etiology or even the pathology, for as yet there have been no necropsy studies reported of patients who have died with this condition.

Since the initial discussion of this syndrome, infrequent case studies have been reported, in which the findings have paralleled to some degree those observed by Morvan. After a review of the available literature, a total of twenty-one case reports was found. Seven of these were included in the original report by Morvan.

Following are the summaries of the remaining fourteen cases, five of which were of adults and nine of children:

Yealland[5] reported a case of a 49-year-old, white male who complained of sores on the right hand. Some thirteen years previously he had observed painless whitlows occurring successively on the little, ring, and middle fingers and the thumb of the right hand. Sensations to pin-prick, heat, and cold were found absent on the right side of the face, neck, upper limb, and thorax as far down as the sixth rib.

Gate and Thevenon[6] described a case with bilateral anesthesia of the hands, contractions of the fingers into hooks, thick, hard, dry skin, and painless infections of the hands. There was a hypesthesia of the right hemithorax and right arm. The presence of a bilateral positive Babinski's sign was the only other abnormal finding of the physical examination. Roentgenograms which revealed an almost total destruction of the distal phalanx of the right thumb were the only abnormal laboratory studies.

Mandeville[7] presented the case of a 45-year-old, Negro female who had osteomyelitis of the left ring finger. Roentgenograms of the hand revealed destruction of the distal phalanx of the thumb as well as that of the ring finger. Two years later the patient complained of a cracking open of the fingers and loss of the finger nails. The following year, atrophy of the muscles of the hands and ulceration of the skin of the fingers were observed. Responses to pain and temperature stimuli were present at that time. The left upper extremity later revealed a brawny swelling of the skin with disuse of the arm. Roentgenograms revealed a Charcot's joint of the left shoulder. There was also atrophy of the distal half of the terminal phalanx of the left thumb and the tips of the terminal

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phalanges of the left index, middle, and ring fingers. There was a persistent flexion deformity of the distal interphalangeal joints, giving the appearance of the "claw-hand" which has been occasionally described in cases of Morvan's syndrome. After several months of a painless, draining infection of the left thumb, a guillotine type amputation was performed on the left forearm. The limited pathologic report presented in this paper revealed nothing which clarified the nature of this disease.

Homans and Thannhauser[8] have discussed the case of a 68-year-old, Italian male who demonstrated a reduced response to pain and temperature stimulation below the knees, ulcers and hyperkeratosis of the feet, mutilation of several phalanges with destruction and distortion of the metatarsal-phalangeal joints, and spontaneous fragmentation of some of the phalanges of both feet. All of the nails of the fingers and toes had an opaque appearance similar to frosted glass. The ulnar nerves were palpable as thickened cords without nodular or spindle-shaped deformities. There was a definite atrophy of the thenar and hypothenar areas and the interossei of both hands. The remainder of the physical examination was not unusual, and the laboratory results were not abnormal. It is doubtful that this represents an example of Morvan's syndrome. The patient had minimal sensory changes and palpable ulnar nerves, which indicate that the condition could be classified in that group of hypertrophic neuridites described by Dejerine and Sottas[8] in 1893.

The most recent report of Morvan's syndrome occurring in an adult was that of a 49-year-old, Negro female seen by Bloom and Moss.[10] This patient was perfectly well until the age of 43 years, when swelling and stiffness of the right upper extremity followed a relatively painless infection of the hand and arm. Shortly thereafter a similar swelling was observed involving the left upper extremity. Several painless ulcers then developed on the fingers. The wrist joints were crepitant but not painful when moved, and the range of motion was good. The response to pain and temperature stimuli was lost in both hands, but light touch and tactile sensations were normal. No muscular atrophies or fibrillations were observed. Roentgenograms showed old, disorganized fractures in both wrists, erosion of the terminal phalanges, soft tissue swelling, and "claw-hand." All laboratory studies were within normal range.

The remaining nine cases represent the total known occurrences of Morvan's syndrome in children. Parks and Staples[11] recently found seven cases in children in the European literature, to which they added two case studies of their own. All of these patients had an onset early in childhood. There was an almost equal involvement of the two sexes. The striking initial disturbance in these patients was the symmetrical loss of sensation to pain and temperature and later to touch sensations in the distal portions of all four extremities. These findings were followed by trophic disturbances of the skin, and atrophy of the bones of the hands and feet with resultant deformity of the nails. Finally, there occurred spontaneous amputations of digits or parts of digits due to the presence of infection. There was no paralysis, muscular weakness, or atrophy observed in these patients. Laboratory studies were not abnormal in any of them.

The following case report in a 2⅓-year-old child presents characteristic signs and symptoms not unlike those previously described, in which the disease first made itself evident at three months of age:

CASE REPORT

D. K., 2⅓ years of age, a white male, was admitted to the Salt Lake County General Hospital on March 1, 1946.

The infant was delivered spontaneously at term and appeared normal. The neonatal period and the two months which followed were not abnormal in any

way. By the end of the third month, however, the nails of the toes and fingers had ceased to grow and three generalized, clonic convulsions occurred in a seven-day period. No trauma or illness was known to be present. Two months later the parents first observed that an older sister was walking on the fingers and hands of the infant without causing him any apparent pain or discomfort. The parents did not become alarmed because the hands appeared normal. At the age of one year the index finger of the left hand was found to be red, swollen, and warm. In spite of apparent soreness of the finger, the child was content to play as usual and used the finger as though nothing were wrong. When the finger was bumped, touched, or manipulated, the child did not cry out or object. No treatment was instituted, and after several days the redness and warmth disappeared, but much of the swelling remained. Six months later a similar painless involvement of the left middle finger was noticed. The local physician was consulted, and the finger was incised. No anesthesia of any kind was used. In spite of this, no sign of distress was expressed by the patient. A small amount of purulent material escaped from the incision and there was very little bleeding. Three months passed before the wound was completely healed. Coincidentally, it was noticed that the nail of the still swollen and somewhat clubbed index finger was much more irregular, convex, and smaller than its fellow of the other hand. The skin of the hands was tough, dry, and firm.

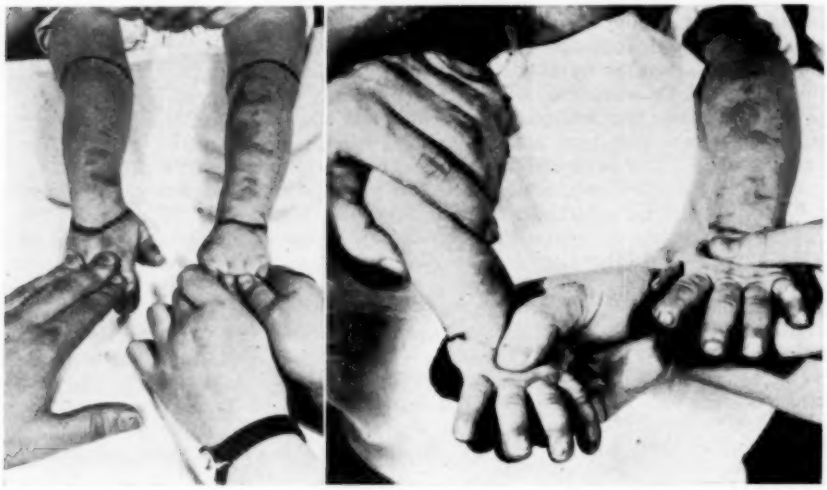

Fig. 1*A*. Fig. 1*B*.

Fig. 1*A*.—Line at wrists indicates limit of area of complete anesthesia. Hypesthesia is present to elbows. Trophic disorder of skin of forearms is shown.

Fig. 1*B*.—Demonstrating blunt terminal phalanges and "claw-like" deformity of left hand.

There were no new developments until five weeks before the next admission. At that time, the patient was admitted to a local hospital with pneumonia. Sulfonamide therapy was instituted, and the response was satisfactory. While in the hospital the child became very irritable, and at times was seen biting his wrists and forearms. The wounds nearer the wrists were deeper, but seemed to be much less painful than those near the elbows. Markings from the bites were still very distinct at the time of discharge from the hospital. Two weeks later, similar markings had appeared high on the arms, and the old areas on

the forearm were much more evident, yet no one had seen him biting himself. A deep laceration was discovered in the distal interphalangeal fold of the left index finger. When the laceration was cleaned and dressed, very little bleeding occurred and the child did not resist or cry. After several days, the laceration had not begun to heal and the markings on the arms and forearms seemed to be spreading. Because of these disturbances the parents brought the child to the Salt Lake County General Hospital for diagnosis and treatment.

His development had been moderately retarded. The patient sat at age 9 months, crawled at age 15 months, began to stand at 18 months, and had walked two or three steps at a time for the previous two months. The child's diet had been adequate and satisfactory in all respects. Immunizations for diphtheria and tetanus were completed in December of 1945. The family history was noncontributory.

Fig. 1*C*.—Limit of hypesthesia is indicated by line above toes.

Physical examination at the time of admission revealed a rectal temperature of 99.8° F.; the pulse was 100, and the respiratory rate 22 per minute. The systolic blood pressure was 88 and the diastolic 58. The height was 33 inches, the weight 24 pounds, and the occipital-frontal circumference 18 inches. The child did not appear acutely ill or distressed. The body size and proportions appeared normal, and the nutrition was good. The patient played cheerfully in the presence of his parents, but soon became irritable when strangers appeared. All tasks requiring the use of the fingers were accomplished with a great deal of difficulty and were awkwardly performed. Except for a mild rhinopharyngitis and hypospadias, the positive findings of the physical examination were limited to the extremities. There were scattered, bright pink, superficial lesions on the dorsal surfaces of the upper extremities from the wrists to the shoulders. These were round or oval in shape, 0.8 to 2.5 cm. in diameter, and had a fine bran-like desquamation near the periphery. The lesions apparently did not itch. The skin of the hands was very dry and thickened, especially on the fingers near the nails and around the old laceration of the left index finger. The margins of the laceration appeared thickened and keratotic, and no granulation tissue could be seen in the wound. The nails of the clubbed index and middle fingers of the left hand were convex and curved over the ends of the fingers. Both nails were much smaller and thicker than those of the corresponding fingers of the right hand. The other nails were wrinkled, thickened, concave, and wider than they were long. The nails of the toes were more normal in shape, size, and thickness, and the skin of the heels and toes was dry

and thick, but elsewhere was not abnormal. The joints of the lower extremities exhibited an exaggeration of range of motion, and the muscles were soft and flabby to palpation.

All of the superficial and deep tendon responses were hypoactive. No pathologic responses were elicited. No muscle weakness, fasciculation, atrophy, or paresis was observed. Except for the fingers, the extremities were symmetrical. There was a definite, bilaterally symmetrical, glove-like area of anesthesia to pain and temperature stimuli. There was a similar lack of response when these same areas were touched with cotton. Areas of hypesthesia extended from the wrists to the elbows, with the greatest reduction of sensation perception distally. Above the elbows there was little if any change observed. Similar disturbances were found in the lower extremities, but to a lesser degree. The toes demonstrated a rather marked hypesthesia to pain and temperature, but response to light touch was present. There was a progressive increase in the degree of response to pain and temperature stimulation to a level just below the knees. All other body areas were apparently not involved.

Fig. 1*D*.—"Claw-like" deformity of left hand is shown. There is no change in bone structure.

Repeated blood studies and urinalyses were normal. All blood cultures remained sterile and blood agglutinations were negative. The blood serum calcium was 10.9 mg. per cent, and the serum phosphorus level was 4.4 mg. per cent. The Mantoux and Kahn tests were negative. Repeated cultures taken from the skin lesions and scrapings obtained from the nails and the laceration of the left index finger were not remarkable. Following is the interpretation of the roentgenograms by Dr. Henry H. Lerner, Head of the Department of Roentgenology of the University of Utah School of Medicine:

"Both hands: There is delayed appearance of the secondary centers of ossification of the metacarpal bones and of the phalanges. There is a "claw" deformity of the left hand with marked inversion of the fifth finger. The bone structure is normal.

"Both feet: There is a delay in the appearance of the secondary centers of ossification of the metarsal bones and phalanges. Both fifth toes show the presence of only two primary centers of ossification for the phalanges. The middle ossification center appears to be missing.

"There is obvious delay in the development of the secondary centers of ossification. The findings place this child in the tenth percentile class (slow) according to the method of Vogt and Vickers."

There was very little change in any of the findings during the thirty-six days of hospitalization. The skin lesions and laceration of the left index finger were much the same at the time of discharge as they were at the time of admission. The child was frequently seen pushing the lacerated finger back and forth across the teeth, causing it to bleed. This did not appear to be painful. The patient could sit, stand, and crawl, but could not walk at the time of admission. A total of ten words were used by the patient, and none of these were ever used in combinations. The entire hospital stay was uneventful, and the patient was discharged to his home on the thirty-sixth day.

CONCLUSIONS

A review of the literature has revealed a total of twenty cases of Morvan's disease. A case of Morvan's syndrome occurring in a 2⅓-year-old male is presented. This child is believed to be the youngest yet reported.

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The Academy Study of Child Health Services

Note: The central office of the Study of Child Health Services has moved to 2346 Massachusetts Avenue, N.W., Washington 8, D. C.

One of the outstanding characteristics of the current Study of Child Health Services is the broad scope of its inquiry. Many excellent and detailed surveys of child health have been made in local areas dealing with limited aspects of the entire field, but never before has there been a similar attempt to gather information pertaining to child health on such a wide scale at one time. From the previous, rather specialized investigations it has been impossible to gain an over-all picture of the situation such as that which is sought by the Academy Study.

When the study was first being organized, there was considerable discussion concerning the advisability of carrying it out on a sampling basis throughout the country. Intensive study of facilities and services in certain selected areas would have greatly simplified the conduct of the study and would have decreased the amount of work involved. The sample technique was abandoned, however, in view of the fact that one of the fundamental purposes of the study has been to stimulate local groups to evaluate services for child health in their own communities. A sampling study would not have yielded sufficiently detailed information for community analysis on a nationwide scale.

In the conduct of the Academy Study, pediatricians, other physicians, and dentists, by virtue of filling out their own questionnaires, have had an opportunity to become familiar with some of the forms used in collecting the desired information. They will thus have become aware of the Series III schedules relating to physicians and dentists in private practice, and some physicians will also have reviewed or assisted in the completion of some of the Series I schedules designed for hospitals and institutions. Although the Series II and IV schedules have been mentioned briefly in earlier articles dealing with the study, the exact content and coverage of all the series have not been published in any detail. It may be of interest to the individual pediatrician and physician, therefore, to learn that the particular schedule which he filled out and returned represents only one of a total of twenty-three schedules. In order to dispel the belief that the questionnaires for those in private practice constitute the full extent of the study, and as a means of indicating the actual scope of the project, a more complete description of all the schedules is presented.

The twenty-three schedules mentioned are divided into four major categories or series representing the four fields of inquiry covered by the study:

SERIES I

Series I schedules seek information regarding facilities, services, and personnel available in hospitals and other institutions which admit children. This series includes eight schedules in all, which are identified as follows:

Schedule I-A. Information on Pediatric Hospitals, General Hospitals and Other Hospitals With Maternity Facilities.—This four-page schedule contains twenty-nine questions including such items as type of ownership, admission policies, type of administration, services rendered, capacity and physical facilities, medical and nursing staff, and departmental organization. This schedule was designed for use in those states where the Commission on Hospital Care Survey did not coincide with the Academy Study.

Schedule I-B and I-C.—In states where a survey under the auspices of the Commission on Hospital Care was in process at the same time as the Study of Child Health Services, information for Schedule I-B was collected in cooperation with the Commission and Schedule

I-C was completed by the transcription of data from the Commission schedules. Thus the data contained in Schedules I-B and I-C combined are identical with those included in Schedule I-A.

Schedule I-D. Supplementary Information on General, Pediatric and Maternity Hospitals With Twenty-Five or More Beds.—In preparing the schedules for the hospitals, an attempt has been made to introduce qualitative as well as quantitative values. For this purpose, the cooperation of the pediatricians themselves has been obtained. Physicians who are familiar with pediatric practice are obviously best qualified to evaluate hospital services for children. Hence, Schedule I-D was prepared with the thought in mind that it should be filled out by a pediatrician at the time of a personal visit to the hospital. This schedule may therefore be considered as a supplement to Schedule I-A, adding qualitative values which would otherwise be lacking.

Schedules I-E Through I-J all relate to special hospitals. Each of these schedules consists of four pages containing items specifically concerned with the accommodations, services and facilities for care of children in the following special fields:

Schedule I-E. Nervous and Mental Hospitals, Including Institutions for the Feeble-Minded.

Schedule I-F. Tuberculosis Hospitals; Sanatoriums and Preventoriums Admitting Tuberculous Patients.

Schedule I-G. Convalescent and Chronic Hospitals, Rest Homes and Nursing Homes.

Schedule I-H. Contagious Disease Hospitals.

Schedule I-J. Orthopedic Hospitals.

SERIES II

Series II includes eight different schedules all concerned with services and facilities for child health provided by public and private health organizations and agencies.

Schedule II. Summary of Public Health Services Available for Children.—As its title indicates, this schedule gives a summary of all official health services for children available in each county, city, state, or local health district.

Schedule II-A. Medical Well-Child Conferences.—A copy of this schedule is being completed by each agency or organization which conducts well-child conferences. The items include admission policy, detailed information concerning types of clinics, personnel, number of sessions held, number of patients seen, type of service rendered, and the location of the conferences.

Schedule II-B. Dental Services for Children.—The information sought by II-B is similar to that concerning the well-child conferences, including a breakdown of the type of dental service rendered to children over a one-year period.

Schedule II-C. Mental Hygiene Services for Children.—Admission policy, specific data on types of cases and services rendered during a one-year period, personnel on staff, and amount of service to other agencies such as schools and welfare organizations illustrate the type of information being obtained on this schedule. The type of cases for which information is sought include mental deficiencies, psychoses, convulsive disorder, delinquents, and behavior problems.

Schedule II-D. Health Services for Physically Handicapped Children.—In addition to background information, II-D is concerned specifically with the number of children and the types of cases seen during one year, including orthopedic, poliomyelitis, cerebral palsy, rheumatic fever, and heart disease. Special attention is paid to the number and work status of professional staff personnel supplying these services.

Schedule II-E. Communicable Disease Control.—II-E includes data on number of immunizations for smallpox, diphtheria, whooping cough, and typhoid, personnel administering service, and special information concerning services by official health agency in relation to communicable disease control.

Schedule II-F. School-Health Services.—II-F covers such items in the school-health program as medical examinations, special examinations including vision, hearing, and tuber-

culosis tests, special services relating to nutrition, psychiatry, speech and so forth, medical and nursing personnel available, nursing services provided, and number of children served by program.

Schedule II-G. Public Health Nursing Services.—II-G relates to the extent and types of nursing service rendered during a one-year period, including number of nurses and the types of programs in which they participate.

SERIES III

Since the three schedules included in this series have been described and distributed widely throughout the country, a detailed description is not needed here. By now almost every physician and dentist in the country will have been at least exposed to one of the three forms which include:

Schedule III-A. Physicians in Private Practice.

Schedule III-B. Pediatricians in Private Practice.

Schedule III-C. Dentists in Private Practice.

SERIES IV

This series of schedules is a fairly recent addition to the study list. So far only two of the proposed three schedules to be included in this series have been developed in final form.

Schedule IV-A. Pediatric Education in Medical Schools.—The first of the detailed schedules dealing with pediatric education is a ten-page folder covering all aspects of undergraduate teaching in all medical schools in the United States. Since this is the first description of these schedules to appear, a complete outline of the contents is presented to illustrate the intensive nature of this important part of the Academy Study.

The main headings of this schedule are as follows:

1. Name and location of medical school.
2. Enrollment of last ten classes.
   a. Enrollment in each of the four academic grades.
   b. Number graduated.
   c. Number of applicants and per cent qualified for admittance to school.
3. Requirements for Admission (excluding wartime accelerated program) including acceptance of women and Negroes.
4. Organization of Department of Pediatrics, including subjects taught and by which department.
5. Staff of department (active), including hours per school year devoted by staff members to various teaching activities.
6. Budget (1946-47), showing source and amount of funds for teaching, research, and other activities.
7. Student hours in pediatrics.
   a. Proportion of time devoted to pediatrics during each of four academic years.
   b. Detailed analysis of subject matter covered, method used, and activities and/or services performed by junior and senior students.
   c. Amount of time and duties of clinical clerkship.
8. Opportunities for observation and practice in care of normal newborn, prematures, special handicaps, convalescents, dental patients, and patients in specialty clinics.
9. Public health activities. Participation of junior and senior students as observers or workers in child health conferences, school health and nursery school programs, children's institutions, etc.
10. Clinical facilities used for teaching.
    a. In-patient facilities. Number of children's beds used for teaching, by type of service in each hospital affiliated with a medical school.
    b. Out-patient facilities. Number of child patients and total children's visits.

11. Special opportunities for work with social service departments on social aspects of disease and on use of community facilities.
12. Facilities available for pediatric pathology.
13. Textbooks used.

Schedule IV-B. Pediatric Education in Hospitals Approved by American Medical Association for Pediatric Residences and Fellowships.—Whereas Schedule IV-A is concerned with the undergraduate teaching of pediatrics in medical schools, Schedule IV-B is intended to evaluate the teaching received by assistant residents, residents, and fellows in the teaching hospitals throughout the country. It would be desirable to include in this portion of the Study all hospitals which have been approved by the American Medical Association for pediatric internships as well as assistant residences and residences. There are so many institutions approved for internships that the amount of effort involved including these did not appear justified. This schedule, therefore, deals primarily with the training received by those who will ultimately become pediatricians.

The items included in this schedule may be summarized as follows:

1. Identification of the hospital with designation of type of ownership and control, and medical school affiliation.
2. The house staff active on the pediatric service.
3. The clinic facilities available for teaching, including premature and newborn care.
4. The number of pediatricians responsible for teaching the house staff, whether on full or part-time and whether or not certified by the American Board of Pediatrics.
5. The number of autopsies and the extent to which residents assist in the pathologic work.
6. The responsibility for routine laboratory work on the part of student, intern, assistant resident, resident, fellow, or technician.
7. Detailed description of the types of experience available to residents on the pediatric service, both in-patient and out-patient.
8. The type of well-child service in which the residents participate.
9. The number of hours spent by residents in teaching conferences, discussion groups, ward rounds, etc.
10. The amount of opportunity available for training in pediatric specialties.
11. The amount of teaching which is done by the assistant residents and residents themselves.
12. Opportunities for research.
13. The responsibility of handling records.

Schedule IV-C. Postgraduate Pediatric Teaching.—This schedule has not yet been prepared in final form. It will be based upon the desire to include in the study information on the quantity and quality of postgraduate teaching, and refresher courses.

When this formidable mass of information is gathered, analyzed, and digested, abundant factual data will be available upon which to base sound plans for the improvement of child health.

The Social Aspects of Medicine

THE UNITED STATES PUBLIC HEALTH SERVICE AND THE DEVELOPMENT OF FEDERAL PARTICIPATION IN HEALTH CONTROL

The communication which follows is a rough résumé full of paraphrase and quotation of a part of Harry S. Mustard's recent book on "Government in Public Health."* The latter gives the history of the development of the various health services in the United States, the local health departments, the state departments of health, and the Federal Health Services, and then describes the status and interrelationships of each in so far as the latter can be defined. His book, which is exceedingly intelligent and interesting, makes one feel that the organization of the Health Services in the United States is as complicated as the English Constitution and, like the latter, is the result of indigenous disconnected growths determined by health problems peculiar to time and place and later brought together and united by a catch as catch can process into a working arrangement. Apparently, health administration in this country sprang up locally and state and federal supervision and control were later developments, the latter following the former. Of the system of health administration as it exists today Dr. Mustard writes, "Not by the greatest stretch of the imagination and sympathetic understanding can it be said that the situation is as it should be. It violates design; it is diffuse; it inhibits coordinated action and invites confusion. And yet, amazingly enough, the individual federal health services function quite efficiently in their respective spheres; and if there is no order in the existing arrangement, there are at least explanations for it." As one reads Dr. Mustard's book, the present system seems to have one advantage: namely, that, with all its obvious imperfections, it possesses great flexibility which permits adjustment to the special needs of localities. This flexibility is due to the loose joints between federal, state, and local control and the ill-defined interrelationships which permit a wide latitude of interpretation and action.

Before proceeding to our special topic, it may be wise to point out that forty other federal agencies participate to some degree in public health or medical care activities. The most important of these are scattered in the Departments of Agriculture, Commerce, Interior, and Labor, and in the Federal Security Agency.

Although I have stated that the Federal participation in the public health services of the country was a late development, the Public Health Service itself dates to 1798. It was born in a manger, so to speak, for at the time of its birth it was a tiny, insignificant premature and nobody conceived how it would grow or what it would become. The seal of the United States Public Health Service consists of a fouled anchor on which is crossed a Caduceus with the date 1798 inscribed below. "That the Caduceus refers to the healing art is obvious; the fouled anchor represents the sailor in distress, and the date indicates the date of enactment of the first Federal law relating to medical care of merchant seamen." As a matter of fact, Alexander Hamilton prepared a report to Congress in 1792, recommending the establishment by the Federal Government of one or more Marine Hospitals as a measure in the interest of humanity in order "to protect from want and misery a very useful and, for the most part, a very needy class of the Community (the sailors of the Merchant Marine)." A bill to this effect was brought before Congress in 1798 by Mr. Livingston of New York. According to it, the relief of the seamen was to be financed by the deduction of twenty cents per month from the wages of each. The President was empowered to appoint Directors of Marine Hospitals in the several ports of the United States and it was the duty of these directors to arrange for hospitalization and provide care for this

*Government in Public Health. Harry S. Mustard, New York City, 1945, The Commonwealth Fund.

particular group and to build Marine Hospitals. No salary was provided for the directors but they were to be reimbursed from Federal funds for necessary expenditures incurred. Each director was responsible to the local Collector of Customs who, in turn, represented the President of the United States. In regard of this act, Falk has written as follows: "This oldest medical service is significant in three respects: (1) it was established for self-supporting, not dependent persons—Americans, seamen and the personnel of the Navy; (2) it was financed by a tax on seamen, by pay-roll deductions from the pay of officers, seamen, and marines in the Navy, and by general taxation; and (3) it included treatment by private physicians and hospital care. As long ago, then, as 1798-99, the principle was accepted that the Federal Government should provide tax-supported medical services and hospitalization for certain classes of independent (non-relief) persons under what was one of the first systems of compulsory sickness insurance in the world." However, as Mustard points out, neither the author of the bill nor the Fifth Congress which passed it, had the clairvoyance to envision and anticipate the great problems in medical care which would come up 150 years later, and the question at issue in their minds was one of expediency in meeting an insignificant problem and not of establishing the foundation of a national system. It is interesting that the bill excited some powerful opposition. Mr. Sewell of Massachusetts doubted the propriety of taxing seamen only for the support of what ought to be considered a public charity. Mr. Varnum of Massachusetts expressed the view that, "It was a business which more particularly concerned the legislatures of the individual states." Mr. Gallatin "was against providing a fund for the purpose by a tax upon labor, which would, in all respects, be a capitation tax." Mr. Pinkney of South Carolina, who supported the bill, thought it "only reasonable and equable that the sailors should pay for the benefit which they were themselves to receive and that it would be neither just nor fair for other persons to pay it." I have gone into this early history in some detail because of its antiquarian interest and, also, because it shows that the legislators then had the same differences of opinion as the physicians today. It is worth noting, also, that the issue was not decided wholly or perhaps chiefly on its intrinsic humanitarian merits but as the result of political expediency. It seemed wise to cultivate and enlarge that useful group of labor and with that end to enact a policy which was an innovation and perhaps an exception never to be repeated.

The act was passed in 1798 but the following year was amended "to provide similar benefits, on a likewise required payment of twenty cents a month, to each sailor and officer of the navy, including the marines. Also, funds collected in one port could be used for relief in another. Apparently, only fragmentary records of development were kept during the first seventy-five years of the Act for the Relief of Merchant Seamen, and such reports as exist indicate that the work did not progress well. Factors contributing to the situation have been summarized by Leigh. "During its first seventy years of activity, the Service had acquired practically all the administrative disabilities associated with Jeffersonian and Jacksonian democracy; its personnel was the object of party spoils, its purchase of supplies was an adjunct to party machinery; its decentralization and lack of central supervision was almost complete; its hospitals were a part of the annual distribution from the Congressional pork barrel; as a means of governmentally supervised sickness insurance it was a fiscal failure requiring annual doles from Congress to keep it solvent and functioning; on account of enforced parsimony it was also very far from offering any guaranty of medical aid to the sailors even at the principal ports."

In 1869, Mr. George S. Boutwell arranged for John Shaw Billings, then a medical officer of the army, to investigate and make recommendations concerning the Marine Hospital Service, and on the Billings-Stewart report was built the act of 1870 by which the Service was reorganized and erected on a national basis. The newly proposed legislation was designated "an Act to reorganize the Marine Hospital Service and to provide for the relief of sick and disabled seamen." It was proposed that the amount deducted from seamen's wages be increased to forty cents a month, that nationalized supervision under medical auspices be provided, and that a supervising surgeon be appointed. Opponents of the bill could see no possible reason for employing a chief medical officer who would be paid a salary to travel over the country at the Government's expense, but the act was passed and

from the administrative standpoint a national service was created. The directing officer appointed happened to be a very able man, Dr. John Woodworth, who had been in health work in Chicago and had served as a surgeon in the Federal Army in the War between the States. He organized the new Corps and its procedures along military line. "He insisted upon searching and impartial entrance examinations, rather completely removed tenure of office and promotion from politics and instituted other sound measures that remain in effect today. In his report of 1874, he devotes a section to "Preventive Medicine in the Service." He wrote, "While the primary object of the Service as defined by statute is the relief of sick and disabled seamen, the duty of preventing, in whatever degree, such sickness and disability is also conceived to be within its scope. Hence preventive medicine, which is receiving from the profession a continually increasing amount of attention, has not been lost sight of in its bearing upon the physical welfare of seamen; and the medical officers of the Service have been invited to study and report upon the conditions of sea life with a view to devising measures for the preservation of the sailor's health and his protection from disease."

The requirement that beneficiaries of the Marine Hospital Service contribute to its support was eliminated by an Act of June 26, 1884. The expenses were to be paid by a special tunnage tax and general taxation. The tunnage tax was eliminated in 1905 and the funds were supplied by the Treasury Department. The system of indirect and contract medical service has become strongly centralized. Part-time physicians have been replaced by full-time medical officers upon a career basis. The beneficiaries were made to include merchant seamen, coast guard personnel, coast guard dependents, coast and geodetic personnel, and a long list of others.

Though the Act for the Relief of Sick and Disabled Seamen was the first Federal Legislation that provided medical care for a certain group of the civilian population, it is generally considered as the nucleus around which the United States Public Health Service developed. However, other laws were passed, giving the Federal Government special nation-wide responsibilities. One act, passed in 1796, provided for Federal cooperation with States and localities in enforcing state and local quarantine relating to ships. Quarantine was regarded as a State function. This act furnished the Federal Government with a basis of authority for making uniform the quarantine procedures at the various ports in the United States. Many members of Congress, however, expressed themselves as being convinced that "Each independent state had a right to legislate on this question for itself. However, constant recurrence of yellow fever epidemics, the memory of the cholera in 1882 and 1873, caused public opinion to demand national enactment in order to prevent the introduction of contagious diseases through the ports. The result of all this was the creation in 1879 of a National Board of Health to have charge of interstate and foreign quarantine. There developed strong opposition to the National Board of Health after its establishment. Dr. Joseph Jones, President of the Louisiana State Board of Health, spoke of "The insolent pretentions of National Board of Health with its odious system of espionage and meddling." But the chief opposition came from the Marine Hospital Service itself, which had been deprived of its quarantine responsibilities. The National Board of Health went out of existence in 1893 after four years, and the quarantine duties were restored to the Marine Hospital Service. 1893 Congress gave the Federal Government further powers, ruling that the regulations of quarantine followed by the various States and ports must be pursuant of or consistent with the Federal law. This Act of 1893 further made provision that if State or municipal health authorities did not have adequate laws, the latter would be supplemented by Federal laws, and if they failed or refused to enforce proper rules and regulations, the Federal Government would have power to supersede them. All State and municipal quarantine stations have been purchased by the Federal Government and all foreign quarantine in the United States is now conducted by the Federal Government.

I have given a brief and fragmentary summary of the history of the development of the United States Public Health Service and of the growth of Federal power in health administration in the country, as recounted by Dr. Mustard, because it is interesting to understand how and why they originated and to realize that the increase in Federal power

by a process of leaps from nil at the beginning has been the result of social and economic necessity. A Federal service of medical care was developed to look after seamen of the Merchant Marine. It was Federal by necessity because the seamen as a class were wanderers and the problem of their care could not be met by the individual states. When the service for seamen was established as a Federal institution, it was easy and natural to extend it to other groups, for example the navy and the marines. As soon as it became apparent that the municipalities at the ports on the eastern seaboard and the states themselves with their varying regulations and systems of operation could not prevent the introduction of yellow fever, cholera, plague, and other diseases, the Federal Government was obliged to intervene for purposes of efficiency by giving itself increased powers. Again it turned to the Marine Hospital Service as the only existing Federal Medical agency. Thereafter, as other problems arose, necessitating unified operation and control or better coordination, laws were passed increasing the Federal prerogatives and at the same time increasing the powers and the scope of action of the United States Public Health Service. And when, finally, Congress embarked on a policy of grants-in-aid to the different states, it turned to the United States Public Health Service and, also, to the Children's Bureau, the latter being a recent development. Now the authors of the Wagner-Murray-Dingell Bill have designated the United States Public Health Service as the agency for the administration of its medical care program on a nationwide basis.

Though we may look askance at the growth of Federal power in this country, in matters pertaining to health and in other things, we are compelled to see that Federal power in public health matters has been increasing ever since this country began. As the country becomes larger and its organization more complicated, increased centralization with its advantages in planning and operation becomes an economic and social necessity. Wherever one looks in Europe, federal governments are being vested with increased power. The social and economic revolution which we are now witnessing and in which we, ourselves, are beginning to be involved, is taking the same form the world over, and in this country has attained far less development than in war-torn Europe with its miseries. But we might as well accept the evil, if you wish, as a fact that the increase in the power of the Federal Government is a world trend, and with new ideas, which carry with them dreams, that medical care can be brought to everyone as his inalienable right. With the advance in medical knowledge and technology, which make such ideas and dreams realizable, increased central direction has become mandatory.

I do not wish to imply that there is or should be no limit to assumption of Federal power in health matters. It seems to me wise to limit it as much as we possibly can without the sacrifice of efficiency and to endeavor as tenaciously as possible to retain the present balanced system of Federal, State, and local health services, which as already pointed out, have great adaptability and latitude though seeming at times intolerably cumbersome and inefficient. After all, they are founded on experience and we ought to hesitate a long time to exchange a system founded on experiences for one founded on theory.

Incidentally, it is interesting to pediatricians to note that a Federal Bureau of Health did exist for four short years and that the United States Public Health Service (the then Marine Hospital Service) was accessory to its murder. It is also interesting to note that the same problems which exist today in regard to the participation of Government in medical activities and the proper means for their support were thought of and discussed by the founders of this country 150 years ago, and that 150 years ago the Federal Government quite unconsciously and in all innocence performed an experiment in medical care which was a poor affair and a failure but had great and splendid consequences. E. A. P.

Academy News and Notes

Two members of the academy have been released from service:

Seymor Fisher, Vt. Benjamin Harrison, Ind. *(Army)*
Thomas M. Lamb, Brooklyn, N. Y. *(Army)*
Daniel J. Pachman, Chicago, Ill. *(Army)*
Samuel Jacob Werlin, Troy, N. Y. *(Army)*
Emmett E. Sappington, San Francisco, Calif. *(U.N.R.R.)*

Dr. Albert P. Knight, who was released from service in the Army, was formerly from Waverly, N. Y., and is now in Tokyo, Japan, in the capacity of Pediatric Consultant to the Department of Public Health and Welfare of General Headquarters of the American Forces Pacific A. C.

News and Notes

The following physicians have been certified in the Sub-Specialty of Allergy by the American Board of Pediatrics in cooperation with the Committee on Allergy of the American Board of Internal Medicine: all certified on record without examination:

Oscar M. Schloss, 125 E. 72nd Street, New York City, N. Y.
Lewis Webb Hill, 319 Longwood Avenue, Boston, Mass.
William Potter Buffum, 122 Waterman Street, Providence, R. I.
Bret Ratner, 50 E. 78th Street, New York City, N. Y.
Jerome Glaser, 300 S. Goodman Street, Rochester 7, N. Y.
Joseph Harman Fries, 25 Plaza Street, Brooklyn 17, N. Y.
John E. Gundy, 264 King Street, Port Chester, N. Y.
Arthur J. Horesh, 10515 Carnegie Avenue, Cleveland, Ohio
Samuel J. Levin, 469 Fisher Bldg., Detroit 2, Mich.
W. Ambrose McGee, 1601 Monument Avenue, Richmond 20, Va.
Benjamin Zohn, 1449 Union Street, Brooklyn 13, N. Y.
Orlindo L. Ross, 9 Exchange Place, Salt Lake City, Utah

Dr. Helen B. Taussig and Dr. Alfred Blalock will together deliver the fifteenth annual series of the Benjamin Knox Rachford Lectureships on Tuesday evening, Feb. 18, and on Wednesday evening, Feb. 19, 1947, at 8:30 P.M., in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati, Ohio. The general title of their lectures will be "Diagnosis, Surgical Treatment, and Results in Congenital Heart Disease."

Book Reviews

Medecine Social de L'Enfance et oeuvres de protection des premier age. Dr. Lucien Garrot, Liege, 1946, Editions Desoer, 364 pages.

A history of the infant welfare movement in Belgium, its development, present status, and a discussion of needs and plans for the future by the medical counsellor of the l'Oeuvre National de l'Enfance. The text discusses infant mortality, its causes and its relation to social conditions. A large part is devoted to the problems and work for the protection of infants in Belgium. One finds that even in so small a country as Belgium where infant health and welfare work is in part private and in part state, there are marked inequalities in the character of the service similar to the conditions which prevail in our own country.

B. S. V.

The Compleat Pediatrician. Fifth Edition. W. C. Davidson, Durham, N. C., 1946, Duke University Press. Price $3.75.

The fact that this is the fifth edition of the Compleat Pediatrician since 1934 testifies to two matters—first, that the practicing pediatrician and physician has found it a most valuable book for rapid reference, and second, that the author has kept pace with the rapid changes in medical knowledge. In this fifth edition the chief changes are in the section on chemotherapy, infectious and tropical diseases about which so much new information and knowledge came out of World War II.

Clinica Y Laboratoria Dr. Gustave Pittaluga (Professor at the institute for scientific investigation of the University of Havana), Havana, 1906. M. V. Fresneda, 459 pages.

A text of clinical laboratory methods with chapters devoted to the blood, urine, serology, functional tests for the liver and kidney, basal metabolism, etc. The bibliography following each chapter shows a thorough knowledge of American as well as Spanish literature.

Acrodinia Infantil. A. Ballabugia Aquado (Chief of the service for infants at the pediatric clinic of the University of Barcelona), 1946, Zaragoza, 95 pages.

A monograph on acrodynia, discussing the etiology, pathology, and clinical manifestations of the disease, with an excellent bibliography of over 250 references.

Opera Paediatrica. R. Academiae Carolinae, Medico-Chirurgicae Holmiensis. I. Jundell, A. Lichtenstein, and A. Wallgren, Upsala, 1945, pp. 629.

A volume of approximately fifty contributions by Swedish pediatricians commemorating 100 years of the pediatric clinic of the Caroline medical school. In 1845, Fredrik Th. Berg became the first professor of pediatrics in any medical school in the world, and started a course of instruction at the Caroline institute which placed pediatrics in Sweden on the same footing as the other branches of medicine. Lichtenstein contributes an interesting first article on the history of pediatrics in Sweden, and properly gives credit to Rosen von Rosenstein as being the "father of pediatrics" and the real founder of pediatrics as a science. Wallgren contributes an essay on "Social Welfare of Swedish Children" and Jundel discusses the pediatric clinics of the universities as centers of medical and medicosocial pediatric care, research, and instruction. These excellent introductory chapters are followed by some forty-odd contributions by Swedish pediatricians. They cover nearly every phase of pediatrics and medical

research. It is interesting to note that 90 per cent of the articles are written in English, which in itself is a matter of historical interest. It is a dignified commemorative volume, giving the picture of the extent and development of pediatrics in Sweden of which our colleagues may well be proud. (The contributions were also published in Acta Paediatrica, vol. 23. Fasc. 3-4.)

B. S. V.

MUSCLE TESTING: Techniques of Manual Examination. Lucille Daniels, Marian Williams, and Catherine Worthingham, Philadelphia, 1946, The W. B. Saunders Company, 189 pages. Price $2.50.

Following the acute state of poliomyelitis the physician-in-charge is naturally apprehensive regarding the prognosis and more specifically, the degree of muscle disability which may eventually ensue. To measure the improvement or lack of it, it has become the custom to institute at an early date a system of muscle testing.

Lovett in 1916 was the first to devise such a system of measurement, and it has stood the test of time remarkably well. However, during the last several years the incidence of polio has increased markedly and with it methods of treatment. It was but natural that the Lovett system of muscle testing should also be modified.

The authors of this little volume have done this in an extremely satisfactory manner. On the left page is an illustration of the relation of a muscle to be tested, its origin and insertion, with a brief discussion of the action of that muscle. On the opposite page is an illustration of the same muscle being tested on a patient. One is a complement of the other, and the effect of this method of presentation is extremely effective.

Those who are called upon to treat muscle deficiency of any kind, who wish to measure progress, or lack of it, will find this manual most helpful.

A pediatrician may not wish to do the actual testing of muscles but with the aid of this manual he will be able to more intelligently discuss his patient with the physical therapist called upon to do the muscle testing.

F. H. E.